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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

IN VIVO MAMMALIAN SHORT-TERM TESTS

1. USE OF THE MOUSE SPOT TEST IN CHEMICAL MUTAGENESIS: INTERPRETATION OF PAST DATA AND RECOMMENDATIONS FOR FUTURE WORK.

Russell LB, Selby PB, Von Halle E, Sheridan W, Valcovic L
Biology Div., Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Mutat Res; 86(3):355-379 1981

The in vivo somatic mutation method in the mouse was developed 23 yr ago using x-rays. Since mid-1970s, 30 chemical compounds have been tested. Unfortunately the seven laboratories now ac tive in the field employ different variations of the method, different criteria for classification and evaluation of the results. Standardization of the method and reporting of results is necessary and standardized protocol is suggested. The establishment of large historical control for common solvents would greatly add to the sensitivity of the assay. The method is potentially useful as a relatively rapid pre-screen for germlike mutagenesis experiments and to detect mutation induction and other events in somatic cells that may be involved in carcinogenesis. The results of 43 chemical compounds tested were compared with previous work. Of the 16 chemicals classified positive in the spot test: 10 were positive carcinogens, six were not done before. Of the six chemicals classified negative: three are positive carcinogens and the other three were not classified. To establish the usefulness of the spot test as a predictor of carcinogenicity, a number of non-carcinogens should be tested. (26 Refs)

2. THE MOUSE SPECIFIC-LOCUS TEST WITH AGENTS OTHER THAN RADIATIONS: INTERPRETATION OF DATA AND RECOMMENDATIONS FOR FUTURE WORK.

Russell LB, Selby PB, Von Halle E, Sheridan W, Valcovic L
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Mutat Res; 86(3):329-354 1981

The mouse specific-locus test with visible markers has been used to study mutations in mammals since 1960. Virtually all reported information was tabulated, statistically analyzed and compared with results obtained in this study testing 25 chemical compounds some of them known carcinogens. Carcinogenicity risk assessment was not intended to be the the function of this test designed to measure mutagenicity per se. (51 Refs)

3. EFFECT OF LONG-WAVE ULTRAVIOLET RADIATION ON MUTAGENIC AND EMBRYOTOXIC EFFECTS OF CHEMICAL SUBSTANCES.

Prokopenko YIu, Il'in VP, Zhurkov VS
A. N. Sysin Inst. General and Communal Hygiene, Moscow, USSR
Gig Sanit; (7):12-15 1981

The modifying effect of long-wave UV radiation on mutagenic effect of cyclophosphamide (CP) and embryotoxic effect of formaldehyde (FD) was studied in random-bred albino mice and rats. Animals were subjected to 1-mo UV irradiation at 0.5 and 3 erythema-inducing doses followed by intragastric administration of test compounds. CP (3, 9 and 27 mg/kg, 5x) caused a dose-dependent increase of the incidence of aberrant metaphases. UV at below erythema dose did not affect the yield of chromosome aberrations, while UV at 3 erythema-inducing doses increased significantly the frequency of aberrant metaphases. FD administration (0.005, 0.05 and 0.5 mg/kg) to pregnant female rats caused a dose-dependent increase of embryolethality. UV at below erythema dose enhanced resistance to FD, while UV at 3 erythema-inducing doses increased embryolethality. (11 Refs) (In RUS)

4. EXPERIMENTAL DATA ON MUTAGENIC ACTIVITY OF TOLUENE, ISOPROPANOL AND SULFUR DIOXIDE.

Aristov VN, Red'kin IuV, Bruskin ZZ, Ogleznev GA
Medical Inst., Omsk, USSR
Gig Tr Prof Zabol; (7):33-36 1981

The mutagenic activity of toluene (TL), isopropanol (IP) and sulfur dioxide was studied in albino rats subjected to a 4-mo inhalation exposure to test substances. Cytogenetic analysis of bone marrow cells showed significantly increased level of aberrant metaphases after exposure to TL and IP. Ineffective concentrations of TL and IP were 2.6 and 0.52 mg/ cubic meter, respectively. (8 Refs) (In RUS)

IN VIVO NON-MAMMALIAN SHORT-TERM TESTS

5. COMPARISON OF PHOTOMUTAGENIC ACTIVITIES OF 5-MOP (BERGAPTEN) AND 8-MOP (XANTHOTOXIN) IN CHLAMYDOMONAS REINHARDII.

Schimmer O
Institut fur Botanik und Pharmazeutische Biologie, Universitat Erlangen-Nurnberg, Schlossgarten 4, D-8520 Erlangen, W. Germany
Mutat Res; 89(4):283-296 1981

The compounds 5-methoxypsoralen (5-MOP) and 8-methoxypsoralen (8-MOP) which are used for photochemotherapy of psoriasis were investigated in terms of their mutagenicity. The photomutagenic and phototoxic activities were compared in arg negative (arg-) cells of Chlamydomonas reinhardii and their ability to revert to Arg+ mutants. 5-MOP was shown to be more phototoxic than 8-MOP if UV-A irradiation (2 W/ square meter (m2) and 2.7 W/m2) was administered to the strains and if the concentration of the compound as well as the original cell number were equal. On the other hand, mutagenicity of both substances increased linearly according to the increase in their concentration if UV-A irradiation was constant. The mutagenic effect of both substances was also dependent on the duration of UV-A irradiation. In both UV-A and white light 5-MOP, however, was effective more rapidly than 8-MOP. Since the minimal effective dose of 5-MOP was reported to be 0.1 ug/ml plus 0.12 Joule/m2, sensitivity of the test object could be compared to that of human lymphocytes in vitro. The minimal effective dose of 8-MOP in human lymphocytes was reported to be 1 ug/ml plus 0.5 Joule/m2. (24 Refs) (In GER)

BACTERIAL TEST SYSTEMS: SALMONELLA

6. EFFECT OF GLUTATHIONE AND URIDINE 5'-DIPHOSPHOGLUCURONIC ACID ON MUTAGENESIS BY BENZO[A]PYRENE AND AFLATOXIN B1 IN THE SALMONELLA/MICROSOME ASSAY.

Malaveille C, Brun G, Hautefeuille A, Bartsch H
Programme of Environmental Carcinogens and Host Factors, Div. Chemical and Biological Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert-Thomas, F-69372 Lyon Cedex 2, France

Mutat Res; 83(1):15-24 1981

The role of the conjugating enzymes, glutathione-S-transferase (GSH-S-T) and uridine 5'-diphosphoglucuronic acid (UDPGA) on rat liver S9-mediated mutagenesis of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in the Salmonella/microsome assay was investigated. In S typhimurium TA100, the UDPGA-dependent reduction of BP mutagenicity was related to the liver S9 concentration: max reduction (40%) in mutagenicity was noted with an S9 concentration of 50 ul/plate. In liquid assays, the presence of 2.5 milliM UDPGA for 20 min caused a two-fold increase in BP mutagenicity at a concentration of 40 uM BP. At 20 uM BP, the presence of UDPGA either did not change or decreased mutagenicity of BP; after 30 min of incubation, a significant decrease was observed. With 20 and 40 uM BP, the addition of GSH to the assays decreased BP mutagenesis by 1.8-and 1.5-fold in the presence of 17% and 9% (vol/vol) liver S9, respectively. GSH had no effect at two-fold lower concentrations of BP. The effect of glutathione (GSH) on AFB mutagenesis was dependent on its concentration. AFB mutagenicity decreased at concentrations of AFB greater than 7.5 nanoM; at 30 nanoM AFB, the AFB mutagenesis was reduced by 1.8-fold. In liquid assays, in the presence of 4.4% S9 from untreated rats the addition of 10 milliM GSH changed the AFB mutagenesis only at concentrations greater than 100 nanoM, resulting in an enhancement of AFB mutagenicity. (43 Refs)

7. FRAMESHIFT MUTAGENESIS OF 9-AMINOACRIDINE DERIVATIVES IN SALMONELLA TYPHIMURIUM.

Young PR, Ma RI, Marfey P, Kallenbach NR
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111

Mutat Res; 90(1):1-10 1981

A number of 9-aminoacridine derivatives with various substituents on the exocyclic amino group were tested in the absence of activation by rat-liver microsomes in order to determine the effect of the substituents on frameshift activity and specificity. The four acridine derivatives tested were 9-aminoacridine, a spin-labeled 9-aminoacridine derivative (4-(9-acridinylamino)-2,2,6,6-tetramethyl-1 piperidinyloxy), quinacrine dihydrochloride, and the putative bisintercalator N,N'-bis(2-methoxy-6-chloroacridine)-tetraethyl enephetamine pentahydrochloride. Frameshift mutagenesis of the acridines was sequence-specific in that significant activity occurred only with the two strains with a +1 frameshift his C (Salmonella typhimurium strains TA1537 and TA1977) and not with the two strains in which reversion was required at a +2 frameshift in his D (TA1538 and TA1978). Excision repair via uvr B was involved only to a minor extent in the production of a frameshift reversion at the his C locus by the four compounds tested. The dose-response of frameshift reversion at his C induced by the acridine was nonlinear. These results are consistent with a model derived from nuclear magnetic resonance experiments on 9-aminoacridine binding to dinucleoside phosphates, in which the N-H group is situated in the duplex so as to participate in a hydrogen bond with one base while excluding its complementary partner, thereby provoking mismatching. (18 Refs)

8. A COMPARISON OF AFLATOXIN B1-INDUCED CYTOTOXICITY, MUTAGENICITY AND PROPHAGE INDUCTION IN SALMONELLA TYPHIMURIUM MUTAGEN TESTER STRAINS TA1535, TA1538, TA98 AND TA100.

Wheeler L, Halula M, Demeo M
Dept. Pharmacology and Dental Res. Inst., Univ. California, Los Angeles, CA, 90024

Mutat Res; 83(1):39-48 1981

Aflatoxin B1 (AFB1) was studied for its ability to induce mutagenesis, prophage induction and cytotoxicity in Salmonella typhimurium tester strains TA1535, TA1538, TA98, and TA100. The frame-shifter tester strains TA1538 and TA98 were susceptible to the lethal effects of AFB1 at all doses tested (up to 1,000 nanog) compared to the base-pair tester strains TA1535 and TA100. The differences were statistically significant at 0.1 and 1 ug. Survival in TA98 was not enhanced by the plasmid pKM101 compared to TA1538, but it did enhance survival of TA100 compared to TA1535. SL1027 (a dihydrostreptomycin-resistant indicator organism), and nalidixic acid resistant strains of Q1, Q1 (Fels 1) and Q1 (Fels 2) were constructed for use as phage indicator strains in the Salmonella inductest. Induction of both prophages, Fels 1 and Fels 2, was observed on the appropriate Q1 lysogen after treatment of TA1535 and TA100 with AFB1 (100 nanog or 1 ug) with S9 mix and cofactors. With TA1538 and TA98, prophage, only one phage was observed, Fels 2. These data demonstrate that prophage induction detects DNA damage induced by liver-activated AFB1 in TA1535 and TA1538 that is non-mutagenic in these histidine auxotrophs. Prophage induction may be a useful tandem assay with other standard microbial tests. (27 Refs)

9. RELATIONSHIP OF THE RAW WATER QUALITY TO MUTAGENS DETECTABLE BY THE AMES SALMONELLA/MICROSOME ASSAY IN A DRINKING-WATER SUPPLY.

Grabow WO, Van Rossum PG, Grabow NA, Denkhaus R
Natl. Inst. Water Res., Council for Scientific and Industrial Res., P. O. Box 395, Pretoria 0001, South Africa

Water Res; 15(9):1037-1043 1981

The relationship of mutagens detectable by the Ames test to other properties of the Parys, South Africa drinking water supply before and after conventional treatment was studied. The raw water intake was from the Vaal River, subject to pollution with partially purified waste water (nonchlorinated) containing high concentrations of mutagens. Information was obtained on mutagen activity, mutagen formation during conventional water treatment, properties of raw water affecting mutagen concentration in the treated water, and the relation of Ames test results to chemical quality parameters. Mutagens formed during treatment consisted mainly of neutral organic compounds inducing frameshift mutations without liver activation. Although no health hazard was inferred, the results make evident the need for surveillance of potential carcinogens in conventionally treated water taken from a polluted source. (33 Refs)

10. MUTAGENICITY OF AMIDE TYPE AND CARBAMATE TYPE DIAZOALKANE-GENERATING AGENTS IN SALMONELLA/MICROSOME ASSAY.

Morita T, Sawaki M, Mifuchi I
Shizuoka Coll. Pharmacy, 2-2-1 Oshika, Shizuoka, 422, Japan
Chem Pharm Bull (Tokyo); 29(6):1758-1762 1981

Both amide type and carbamate type N-nitroso compounds, which have a common structure and have been reported to be excellent diazoalkane-generating compounds were examined for mutagenicity by measuring their ability to create histidine (his) prototrophic revertants of two his-dependent Salmonella typhimurium strains: T100 (a base-pair substitution strain) and TA98 (a frameshift strain), with and without metabolic activation by S-9 mix. Six compounds of each type having systematic substitutions at two different sites of the basic common structure were examined systematically over dose ranges of 0.27-2.7 umole (4 x 10(-5) to 4 x 10(-2) M). In the absence of activation, none of the amide type compounds showed any mutagenicity in either strain. With metabolic activation, two of six amide type compounds (both having a benzyl group in the same position) were weakly mutagenic to TA100. In the absence of S-9 mix, only one of six carbamate type compounds showed any mutagenicity (against TA98); in the presence of S-9 mix, all six carbamate compounds were mutagenic against TA100 over a wide range of concentrations and two of six were weakly mutagenic against TA98. There is apparently a structure-mutagenicity relationship for amide type and carbamate type compounds that is principally dependent upon the rate of chemical generation of diazoalkane or phenyldiazomethane in alkaline soln. (8 Refs)

11. MUTAGENICITY OF REACTION PRODUCTS OF SULPYRINE WITH NITRITE.

Sakai A, Yoshikawa K, Tanimura A, Tomita I
Div. Food Additives, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo, Japan
Mutat Res; 90(1):57-65 1981

The mutagenicity of three N-nitroso products of sulpyrine (1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide hydrate (DPMN), 4-(N-methyl-N-nitroso)aminoantipyrine (MNAA), and 1-acetyl-1-methyl-2-nitroso-2-phenylhydrazine) and of related compounds (4-methylaminoantipyrine, 1-acetyl-1-methyl-2-phenylhydrazine, 4-hydroxyantipyrine, sulpyrine, and sodium nitrite) was tested on Salmonella typhimurium TA100 and TA98. DPMN, MNAA, and sodium nitrite were mutagenic to TA100 but not to TA98. None of the other compounds were mutagenic to either strain. Activation of mutagenicity with rat-liver microsomal preparation (S9 mix) was required by MNAA, but not by DPMN. The addition of L-cysteine or glutathione markedly increased the mutagenicity of DPMN; the enhancing effects were proportional to concentration added. The possibility that sulpyrine might pose a carcinogenic hazard in man is discussed. (25 Refs)

12. FLUORO-SUBSTITUTED N-NITROSAMINES. 1. INACTIVITY OF N-NITROSO-BIS-(2,2,2-TRIFLUOROETHYL)AMINE IN CARCINOGENICITY AND MUTAGENICITY TESTS.

Preussmann R, Habs M, Pool B, Stummeyer D, Lijinsky W, Reuber MD
German Cancer Res. Center, Inst. Toxicology and Chemotherapy, Heidelberg, W. Germany
Carcinogenesis; 2(8):753-756 1981

The LD50 of N-nitro-bis-(2,2,2-trifluoroethyl)amine (NBTFA) was determined to be 300 mg/kg in male Sprague Dawley rats. To test the carcinogenicity of NBTFA, rats were fed 3 mg NBTFA/kg body wt/day. They were observed for their lifetime or until killed when moribund. Fischer 344 female rats were fed 3.7 mg NBTFA, 1.8 mg diethylnitrosamine (DEN), or 0.7 mg DEN/kg/day. Treatment lasted 30 wk. Animals were allowed to die naturally. In both Sprague Dawley and Fischer rats, chronic treatment with NBTFA was found to have no carcinogenic effect. An equimolar amount of DEN produced 100% incidence of tumors and was tumorigenic at much lower levels. Mutagenicity tests with Salmonella typhimurium strains TA1535 and TA100 with activation by rat hepatic S-9 fraction were negative. Apparently the presence of fluorene in the beta position of the DEN-derived NBTFA molecule blocks the alpha-oxidation thought to be necessary for the activation of carcinogenicity and mutagenicity of dialkylnitrosamines. (17 Refs)

13. BACTERIAL MUTAGENICITY AND TOXICITY OF CYCLOALIPHATIC EPOXIDES.

Frantz SW, Sinsheimer JE
(c/o Sinsheimer) Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109
Mutat Res; 90(1):67-78 1981

The Ames mutagenicity test with Salmonella was used to investigate mutagenicity of 12 cycloaliphatic epoxides without the addition of liver homogenate fractions. Eight compounds exhibited base-pair substitution mutagenic activity. Mutagenicity decreased with expanding ring size, while inhibition of bacterial growth increased with increasing ring size. Epoxide toxicity at the doses required for mutagenicity prevented establishment of meaningful dose-response relationships. Petri dish sealing bands were used to prevent loss of volatile compounds during 48 hr incubation. Mutagenicity was greater in TA1535 than in TA100; toxicity was more pronounced in TA100. Toxicity was not reduced by the use of less permeable strains (TA92, TA1950, and TA2410). Cyclooctane oxide testing with TA1975 (repair-proficient) and TA1535 (repair-deficient) demonstrated that the bacteria were not being killed by damage to DNA, since toxicity was not reduced in TA1975. The results confirm that cis-1,2-disubstituted oxiranes are mutagenic. (26 Refs)

14. MUTAGENIC ACTIVITY OF CAFFEINATED AND DECAFFEINATED COFFEE.

Kam JK
Univ. California, Berkeley, CA, 94720
Cancer Detect Prev; 3(2):507-511 1981

Two types of coffee (caffeinated and decaffeinated) were tested for their mutagenicity using bacterial strains using TA98 and TA100 in Ames Salmonella/Microsome test. According to the Ames criteria, both were found to be mutagenic in the absence of S-9. The mutagens did not require liver enzymes to be activated. (Author abstract) (13 Refs)

15. MUTAGENICITIES OF CARBADOX AND OLAQUINDOX - GROWTH PROMOTERS FOR PIGS.

Yoshimura H, Nakamura M, Koeda T, Yoshikawa K
Second Assay Div., Natl. Veterinary Assay Lab., 1-15-1 Tokura, Kokubunji-shi, Tokyo 185, Japan
Mutat Res; 90(1):49-55 1981

Both carbadox and olaquindox were positive in the Bacillus subtilis rec and in the Salmonella typhimurium uvr repair tests. In the reverse mutation test with S typhimurium TA100 and

TA 98, a linear dose-response relationship was observed for both compounds between 0 and 15 ug/plate. Carbadox was more mutagenic than olaquindox and their activities were marked with strain TA100 (respectively, 315.4 vs 46.3 revertants/ug). In the absence of microsomal supernatant (S9), carbadox was approx 6x more mutagenic than olaquindox; in TA100 with S9, the number of revertant colonies decreased to 146.8/ug with carbadox but only to 38.3/ug with olaquindox. S9 incubation inactivated carbadox almost totally after 10 min, whereas olaquindox retained its activity after 20 min. Carbadox required 20 min to be inactivated by a bacterial cytosol mixture; olaquindox was hardly inactivated after 60 min. Carbadox and olaquindox appear to induce frameshift and base-pair substitution mutations as a result of error in the DNA repair process. Significance of the findings is discussed with respect to use of these compounds as growth promoters in pigs. (18 Refs)

16. A PROCEDURE FOR THE QUANTITATIVE MEASUREMENT OF THE MUTAGENICITY OF VOLATILE LIQUIDS IN THE AMES SALMONELLA/MICROSOME ASSAY.

Barber ED, Donish WH, Mueller KR
Health, Safety and Human Factors Lab., Eastman Kodak Co., Rochester, NY
Mutat Res; 90(1):31-48 1981

Development and application of an apparatus which allows quantitative study of the distribution and mutagenicity of volatile test chemicals is reported. The containment system is made of materials which are chemically inert with respect to halogenated hydrocarbons. Containment properties of the system were examined using 14C-1,2-dibromoethane and gas liquid chromatographic analysis; 95% of the chemical remained after 48 hr incubation at 37 C. Only two significant solvent compartments were found (the vapor and aqueous phases); use of plastic plates significantly perturbed solvent distribution within the container. Using the Ames Salmonella assay with strains TA1535, TA1537, TA98, and TA100, 10 common haloalkane solvents were tested in the system. Of the 10 compounds, only 1,2-dibromoethane and 1-bromo-2-chloroethane gave positive responses in the standard plate incorporation test; their potencies were approx 1/20-1/50 that determined in the closed system. In the closed system 7/10 compounds exhibited some degree of activity. Mutagenic potencies ranged between 0.001 (1,2-dichloroethane) and 0.172 revertants/nanomole (1,2-dibromoethane). The closed system reduces solvent exposure of personnel and the chance of false positives due to mutagenic impurities. It may provide better simulation of actual (vapor phase) exposure. (27 Refs)

17. FRAMESHIFT MUTATIONS: RELATIVE ROLES OF SIMPLE INTERCALATION AND OF ADDUCT FORMATION.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):21-30 1981

The mutagenic properties of 9-aminoacridine, its derivative quinacrine, and the nitro-containing derivative Entozon were examined in Salmonella typhimurium and Escherichia coli WP2uvrA assays. Both 9-aminoacridine and quinacrine induced frameshift mutations in strain TA1537 only (with, respectively, 1.7 and 3.0 revertants/nanomole (r/nm)), confirming the finding that simple intercalators mutate this strain alone. Entozon primarily affected strains TA98 (338 r/nm) and TA1538 (288 r/nm), indicators for frameshift mutations resulting from adduct formation; mutagenicity was greatly decreased when Entozon was tested in strain TA1978 (23 r/nm), the uvrB+ analog of TA1538 which does not respond maximally to the mutagenic action of adduct-forming chemicals as a result of its intact uvrB system. Entozon displayed no base-substitution activity for Salmonella, although it exhibited some activity when tested in E coli WP2uvrA (2.4 r/nm). When a cell is exposed to a molecule inducing frameshift mutations by intercalation and adduct formation, the formation of adducts apparently exerts a much stronger influence on total mutagenic expression. (47 Refs)

18. EFFECTS OF HARMAN AND NORHARMAN ON THE METABOLISM OF ANILINE AND P-DIMETHYLAMINOAZOBENZENE.

Hayashi K
Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan
Nippon Eiseigaku Zasshi; 36(2):495-50[illegible] 1981

The metabolism and mutagenicity of aniline and p-dimethylaminoazobenzene (p-DAB) were studied in vitro using rat liver microsomes. In the absence of harman (l-methyl-9H-pyrido[3,4-b]indole) and norharman (9H-pyrido[3,4-b]indole), p-DAB was metabolized to aniline without accumulation of p-methylaminoazobenzene (p-MAB) or p-aminoazobenzene (p-AAB). Aniline was metabolized to p-aminophenol (p-AP). Harman or norharman substantially inhibited metabolism of aniline to p-AP in microsomes. Norharman was a greater inhibitor than harman. Norharman slightly reduced the metabolism of p-DAB to aniline and caused the accumulation of p-DAB, p-MAB, and p-AAB. The metabolites of aniline, o-aminophenol, m-aminophenol, p-AP, and nitrosobenzene, were tested for mutagenicity in Salmonella typhimurium TA98. Nitrosobenzene was mutagenic only in the presence of norharman with S-9 mix. Similarly p-MAB, p-AAB, and aniline were mutagenic in TA98 only in the presence of norharman with S-9 mix. Harman and norharman each greatly inhibited aniline hydroxylase activity, while aminopyrene demethylase had only a slight effect. Aryl hydrocarbon hydroxylase was inhibited by norharman, but not by harman. (23 Refs) (In JPN)

19. MUTAGENICITY OF THE TWELVE IMIDAZOLE COMPOUNDS WITH ANTITRICHOMONAL ACTION.

Belisario MA, Quintol, De Lorenzo F
II Istituto di Chimica Biologica, Universita di Napoli, Napoli, Italy
Boll Soc Ital Biol Sper; 57(7):805-809 1981

Some imidazole compounds were reported as mutagens and carcinogens. All 12 compounds tested by Ames' Salmonella method were mutagenic. There was no correlation between mutagenicity and antitrichomonal action. (17 Refs) (In ITA)

20. MUTAGENICITY OF QUINDOXIN, ITS METABOLITES, AND TWO SUBSTITUTED QUINOXALINE-DI-N-OXIDES.

Beutin L, Preller E, Kowalski B
Unite d'Immunoparasitologie, Institut Pasteur, 75724 Paris Cedex 15, France
Antimicrob Agents Chemother; 20(3):336-343 1981

The quinoxaline-di-N-oxides carbadox, olaquindox, and quindoxin, which are potent antibacterial agents, were tested for mutagenicity in the Salmonella microsomal system. They all induced base pair substitutions and frameshift mutations in Salmonella, and occurred independently of the presence of rat liver microsomal fraction in the test system. Mutagenicity was dependent on the presence of their N-oxide groups, since quinoxaline, a completely reduced derivative of quindoxin, was not mutagenic, whereas the partially reduced quinoxaline-N-oxide exhibited a lower mutagenic activity than quindoxin. recA and uvrB Salmonella were found to be more susceptible to mutagenic quinoxaline derivatives than wild-type strains. The mutagenicity of quinoxaline-di-N-oxides was enhanced under anaerobic incubation as was the antibacterial activity. These results suggest that both the antibacterial and mutagenic activity of quinoxaline-di-N-oxides depend upon the same bacterial activation mechanism. (Author abstract) (26 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: MUTAGENICITY

21. DETECTION OF MAMMALIAN CELL MUTAGENS IN URINE FROM CARCINOGEN-DOSED MICE.

Amacher DE, Turner GN, Ellis JH
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Mutat Res; 90(1):79-90 1981

Urine was collected from male CD-1 mice dosed by oral gavage with either 300 mg/kg 2-aminofluorene (AF), 150 mg/kg cyclophosphamide (CY), or 200 mg/kg lucanthone (LU), and added directly to L5178Y TK+/- mouse lymphoma cultures (heterozygous at the thymidine kinase locus for the induction of trifluorothymidine-resistant (TFT-R) mutants). After 3 hr incubation, urine from the three different groups of rats produced significant, dose-dependent increases in frequency of TFT-R mutants. When the drugs were tested directly as mutagens in L5178Y TK+/- cells, LU and CY were positive both with and without metabolic activation, but AF required activation. Significant differences in the direct response of Salmonella typhimurium and L5178Y cells to these compounds indicate that the two cell types may not detect the same chemical entities as proximate mutagens. Urinary metabolites of AF, CY, and either the parental molecule or metabolites of LU can readily be detected as mutagens in a mammalian cell assay. (28 Refs)

22. MUTAGENICITY OF N-ALKYL-N-(ALPHA-ACETOXYALKYL)NITROSAMINES IN V79 CHINESE HAMSTER CELLS IN RELATION TO ALKYLATING ACTIVITY.

Huang GF, Mochizuki M, Anjo T, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):531-538 1981

Mutation to ouabain resistance and cytotoxicity were tested in V79 Chinese hamster cells after the cells had been treated for 2.5 hr with a series of N,N-dialkylnitrosamines (alkyl = methyl, ethyl, propyl, butyl or tert-butyl) monosubstituted at the alpha-carbon with an acetoxy group. The effects of the length of alkyl chain and the mode of substitution with the acetoxy group on the cytoxicity and mutagenicity were examined. In the series of N-alkyl-N-(acetoxymethyl)nitrosamines with an acetoxy group at the primary alpha-carbon, the methylating compound N-methyl-N-(acetoxymethyl)nitrosamine was the most cytotoxic and mutagenic, and the biological activities decreased in the order of ethyl, butyl and propyl homologs. N-tert-Butyl-N-(acetoxymethyl)nitrosamine was not mutagenic at the concentration tested. At equitoxic concentration, N-ethyl-N-(acetoxymethyl)nitrosamine was found to be the most mutagenic. Of the two N-alkyl-N-(alpha-acetoxybutyl)nitrosamines having an acetoxy group at the secondary alpha-carbon, N-methyl-N-(alpha-acetoxybutyl)nitrosamine was more cytotoxic and mutagenic than N-butyl-N-(alpha-acetoxybutyl)nitrosamine. A comparison of the corresponding N-alkyl-N-(acetoxymethyl)nitrosamines and N-alkyl-N-(alpha-acetoxybutyl)nitrosamines showed that the latter had stronger activities. A plot of the mutation frequency versus the ability of the alpha-acetoxy compounds to alkylate 4-(p-nitrobenzyl)pyridine was linear. This indicates that the chemical reactivity of the compounds plays an important role in inducing mutation in V79 Chinese hamster cells. (Author abstract) (26 Refs)

23. RAT HEPATOCYTE-MEDIATED MUTAGENESIS OF HUMAN CELLS BY CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS BUT NOT ORGANOCHLORINE PESTICIDES.

Tong C, Fazio M, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 167(4):572-575 1981

The establishment of a hepatocyte primary culture-mediated human cell hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutagenesis assay is reported. In the rat hepatocyte primary cultures (HPC)-mediated Detroit 550 (D-550) HGPRT mutation assay, 1 x 10(6) D-550 were generally coplated with 20 x 10(6) freshly prepared HPC. The cocultures were allowed to attach for 2 hr, were washed, and fresh media containing the carcinogens or appropriate controls were added for 24 hr exposure. The cultures were washed then allowed to grow for 10 days to allow mutant expression. In general, by day 4, no viable HPC were observed. HGPRT mutants were selected in the human foreskin cell line D-550 by 6-thioguanine (TG). Exposure of D-550 alone to benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene did not result in any increase in TG-resistant (TGr) mutant incidence over the parallel-run control. However, a significant increase in the TGr mutant incidence over that in control cultures occurred in D-550 when the carcinogen exposure was in the presence of HPC. With dichlorodiphenyltrichloroethane, chlordane, and mirex, no significant increase in TGr mutant incidence was observed in the exposed human cells either in the presence or absence of HPC. An epigenetic mechanism for the carcinogenicity of these organochlorine pesticides is suggested. (34 Refs)

24. A SIMPLIFIED METHOD FOR MEASURING SCHEDULED AND UNSCHEDULED DNA SYNTHESIS IN HUMAN FIBROBLASTS.

Agrelo CE
Seccion de Toxicologia, Departamento de Farmacologia, C.I.E.A. - I.P.N., Apdo. Postal 14-740, Mexico City 14, D.F., Mexico
Toxicology; 21(2):151-158 1981

Experiments were carried out to attempt to develop a simple, rapid method to assay unscheduled DNA synthesis (UDS) that could serve well in large-scale screening studies for carcinogenic activity. Tritium-labeled thymidine incorporation into normal human fibroblasts (HF) and into HF blocked DNA synthesis by hydroxyurea (HU) was measured in the presence of a variety of known carcinogens, precarcinogens, and noncarcinogens. Positive results (a dose-related increase in UDS in the treated inhibited cells greater than 2x that in control inhibited cells) were obtained with most of the carcinogens and negative results with most of the noncarcinogenic compounds.

The method compares favorably with other more difficult and time-consuming UDS assays. (15 Refs)

25. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' re pair of 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the limit of resolution of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

26. BROMODEOXYURIDINE PHOTOLYSIS ASSAY AS A POTENTIALLY USEFUL METHOD FOR ASSESSING DNA DAMAGE AND ITS REPAIR INDUCED BY ULTRAVIOLET LIGHT.

Yatani R, Konishi T, Kusano I, Shiraishi T, Noda M, Ohashi S, Suzuki M
Dept. Pathology, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):267-272 1981

The bromodeoxyuridine (BrdUrd) photolysis assay was used to assess DNA damage and repair induced by UV light in three melanoma cell lines, xeroderma pigmentosum (XP), normal human fibroblasts, and HeLa S3 cells. The cells were incubated with 3H-thymidine or 14C-deoxythymidine for 24 hr, incubated in nonradioactive medium for 2 hr, then exposed to 20 Jm-2 of a 254 nanometer (nm) UV light. The cells were then incubated for 24 hr in medium containing hydroxyurea and BrdUrd or deoxythymidine. BrdUrd incorporated into DNA during the repair period by exposing the cell suspension to a 313 nm light. Postreplication repair assays were also conducted. In normal cells, a UV-induced lesion in the DNA was necessary before incubation in BrdUrd synthesized DNA to 313 nm radiation and a UV-induced lesion resulted in the incorporation of BrdUrd throughout the 3H-thymidine cellular DNA. In XP cells, the incorporation of BrdUrd into the DNA after UV-irradiation was negligible. The marked decrease in sedimentation rate seen in normal human fibroblasts after UV, BrdUrd treatment, and 313 nm irradiation did not occur in XP cells although slight differences in XP cells subjected to such treatment were seen compared with those not UV-irradiated. Normal cells became highly sensitive to 313 nm light when they were permitted to repair UV-induced lesions in the presence of BrdUrd, while XP cells did not have that sensitivity, presumably because they cannot make the initial strand breaks which necessarily precede the incorporation of BrdUrd. This assay detects excision repair as a cumulative process and estimates the patch size involved in repair replication as well as interpatch distances. (26 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: CYTOGENETIC TESTS

27. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr(VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: TRANSFORMATION

28. THE HOW AND WHY OF IN VITRO ONCOGENIC TRANSFORMATION.

Hall EJ, Miller RC
Radiological Res. Lab., Dept. Radiology, Cancer Center, Columbia Univ., New York, NY, 10032
Radiat Res; 87(2):208-223 1981

To provide an estimate of the magnitude of the public health hazard involved in low doses of radiation, various test systems were used for in vitro study of oncogenic transformation. Of various established cell lines, 10T1/2 was found to be the most suitable for low-dose studies. Analysis of the incidence of oncogenic transformation showed a quadratic dependence at doses above 1 Gray (Gy) and linear relationship for doses below 0.3 Gy. Between 0.3 and 1 Gy, the transformation frequency did not vary with dose. Fractionation of the dose was found to increase the transformation incidence. The use of fresh explants of hamster embryos also showed that dose fractionation led to an enhancement of transformation for total doses less than 1.5 Gy and a reduction of transformation for higher doses. It was emphasized that future studies of in vitro transformation should be conducted in the epithelial cells of human rather than rodent origin. (22 Refs)

29. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideration of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

ACTIVATION OF CARCINOGENS FOR SHORT-TERM TEST SYSTEMS

30. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Kaneda S, Seno T, Takeishi K
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JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutagenic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved. (Author abstract) (31 Refs)

31. MODIFICATION OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RATS WITH INDUCERS OF THE CYTOCHROMES P-450.

Hales BF
Dept. Pharmacology and Therapeutics, McGill Univ., Montreal, Quebec H3G 1Y6, Canada
Teratology; 24(1):1-11 1981

The chemotherapeutic agent cyclophosphamide (CP) may act as a carcinogen if it is enzymatically metabolized to reactive intermediates with alkylating, mutagenic, or cytotoxic effects, which activation is thought to be catalyzed by the cytochrome P-450 monooxygenase system. Phenobarbital (PB) induces the hepatic cytochrome P-450 that is involved in the activation of CP to both alkylating and mutagenic metabolites; beta-naphthoflavone (bNF) induces a different cytochrome P-450 and actually decreases the activation of CP by liver microsomes. Using rats pretreated with either PB or bNF, the activation of CP to mutagenic metabolites by enzyme fractions on day 13 of gestation was measured with the Ames test on Salmonella typhimurium TA1535 and teratogenicity was assessed in vivo by treatment of rats with CP on day 13 of gestation. CP was activated to mutagenic metabolites to the same extent (on a tissue wet wt basis) by enzyme fractions from maternal liver, kidney, and placenta, despite differences in cytochrome P-450 content, but fetal homogenates did not activate CP. PB pretreatment increased the liver cytochrome P-450 content 1.8-fold and the activation of CP by maternal liver microsomes 10-fold; however, PB did not alter the activation of CP by maternal kidney, by placenta, or by the fetus. PB pretreatment increased the teratogenicity of CP as measured by an increased incidence of malformed embryos or by decreased fetal wt. Pretreatment with bNF did not induce the hepatic cytochrome P-450 in the pregnant rat; did not change the activation of CP to mutagenic metabolites by liver, kidney, the placenta, or the fetus; and had no effect or decreased the teratogenicity of CP. These results suggest that the mother, rather than the fetus, is the site of PB activation; that the principal site of activation is the maternal liver; and that there is a correlation between the teratogenicity and mutagenicity of CP after induction by cytochrome P-450. (36 Refs)

COMPARATIVE RESULTS FROM MULTIPLE TEST SYSTEMS

32. ONCOGENIC TRANSFORMATION AND CELL LYSIS IN C3H/10T1/2 CELLS AND INCREASED SISTER CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY NICKEL SUBSULFIDE.

Saxholm HJ, Reith A, Brogger A
Inst. Pathology, Univ. Oslo, Rikshosptalet, National Hosp., Oslo, Norway
Cancer Res; 41(10):4136-4139 1981

We have scored frequency of transformation and appearance of the oncogenic marker 'long microvilli' in mouse embryo fibroblast C3H/10T1/2 cells in culture for the compound Ni3S2. Furthermore, we have scored for Ni3S2-induced sister chromatid exchange in cultured human lymphocytes. Nickel subsulfide in moderate doses caused morphological transformation to Type I, II, and III foci and induced long microvilli on the cells in the transformed cultures, demonstrating oncogenic transforming ability. Higher doses led to cell lysis after a lag period. The carcinogenic potency of Ni3S2 in this system was not as strong as that of methylcholanthrene. Ni3S2 increased the sister chromatid exchange frequency in human lymphocytes in a marginal, not dose-dependent way. The increased sister chromatid exchange may indicate that the carcinogenic effect of Ni3S2 is genetic rather than epigenetic. (Author abstract) (39 Refs)

33. DIFFERENTIATION OF THE MECHANISMS OF ONCOGENICITY OF 1,4-DIOXANE AND 1,3-HEXACHLOROBUTADIENE IN THE RAT.

Stott WT, Quast JF, Watanabe PG
Toxicology Res. Lab., Dow Chemical U.S.A., Midland, MI, 48640
Toxicol Appl Pharmacol; 60(2):287-300 1981

Two tumorigenic agents, 1,4-dioxane (DX) and 1,3-hexachlorobutadiene (HCBD) were compared to the known mutagen dimethylnitrosamine (DMN) to determine whether their actions were by a genetic or nongenetic mechanism. Male Sprague Dawley rats were given tumorigenic doses of DX in drinking water (0, 10 or 100 mg/kg/day for 11 wk), HCBD by gavage (0, 0.2, or 20 mg/kg/day for 3 wk), or DMN by gavage (3 mg/kg/day for 3 wk). Other groups of rats were given single doses of DX (10, 100, 1,000 mg/kg), HCBD (0.2, 20 mg/kg), or DMN (3 mg/kg) by gavage. DX produced no genotoxic effects at tumorigenic doses. A single large dose produced no alkylation of DNA or increase in DNA repair. Repeated high doses of DX were hepatotoxic. HCBD produced a minor genotoxic effect compared with DMN. DNA repair in renal tissue was increased 1.27-1.54-fold by HCBD (20 mg/kg); DNA alkylations occurred at the rate of 0.78 per 10(6) nucleotides. No mutations were produced in the Ames' bacterial mutagenesis assay. HCBD produced renal cytotoxicity. Apparently DX induces tumors by a nongenetic mechanism. HCBD acts primarily in a nongenetic way, but is weakly genotoxic. Risk from either compound is likely only at cytotoxic doses. (34 Refs)

34. MUTAGENICITY OF CHEMICALS OF INDUSTRIAL AND AGRICULTURAL RELEVANCE IN SALMONELLA, STREPTOMYCES AND ASPERGILLUS.

Principe P, Dogliotti E, Bignami M, Crebelli R, Falcone E, Fabrizi M, Conti G, Comba P
Istituto Superiore di Sanita, Viale Regina Elena 299-00161, Rome, Italy
J Sci Food Agric; 32(8):826-832 1981

Ethylene dibromide (EDB), ethylene dichloride (EDC), propylene dichloride (PDC), allyl alcohol (AA), and sulfallate (S) were tested for their ability to induce reverse mutations (his+ revertants) in Salmonella typhimurium, forward mutations (streptomycin resistance) in Streptomyces coelicolor, and point mutations (8-azaguanine resistance) in Aspergillus nidulans. EDB and S strongly reverted S typhimurium strains TA100 and TA1535;, PDC had a weak effect on these strains; and EDC was weakly active in TA1535 following microsomal activation with rat liver S-9 mix. This mix reduced the mutagenicity of EBD but not that of S. In S coelicolor, EDB was positive only in spot test experiments and S was weakly positive in plate tests; EDC and PDC were inactive in both test systems. In A nidulans, EDB and PCB gave positive responses in the plate and spot tests and S gave a positive response only in the spot test. AA was was not mutagenic in any of the genetic systems. (21 Refs)

EVALUATIONS, REVIEWS AND OTHER RELATED STUDIES

35. THE ROLE OF GENETIC TOXICOLOGY IN A SCHEME OF SYSTEMATIC CARCINOGEN TESTING.

Williams GM, Weisburger JH, Brusick D
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:57-87 1981

No single test has been developed for detecting all hazardous chemicals. It is therefore important to formulate the criteria for selecting the best combination of tests for a test battery. A battery should combine detection and confirmation of a hazard in one step. It should be capable of including all types of hazards. The tests should have clear biological significance and should maximize metabolic parameters. The Decision Point Approach involves five sequential steps in evaluating the carcinogenic potential of a chemical. First the structure of the chemical is determined. Then a series of in vitro short-term tests are run. These tests include bacterial mutagenesis, DNA repair, mammalian mutagenesis, sister chromatid exchange, and cell transformation. The evidence provided by the tests is evaluated. A suspected chemical is tested in limited in vivo assays for skin tumor induction in mice, pulmonary tumor induction in mice, breast cancer induction in female Sprague-Dawley rats, and altered foci induction in rodent liver. Further evaluation is made. Chronic bioassays complete the series of tests. A final evaluation of all the tests is made, allowing a decision to be made on the hazard of the chemical in question. (63 Refs)

36. PESTICIDES: MUTAGENIC AND CARCINOGENIC POTENTIAL.

Waters MD, Nesnow S, Simmon V, Mitchell AD, Jorgenson TA, Valencia R
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
ACS Symp Ser; 160:89-113 1981

A phased approach has been developed for evaluating the mutagenic and carcinogenic potential of chemicals. The method combines cost-effective use of limited testing facilities with protection from hazards to human health. Since no single test is capable of detecting all hazardous chemicals, proper testing requires the minimum number of tests which will effectively reveal mutagenic and carcinogenic properties. Phase I involves detection. Short-term bioassays emphasize point mutations and primary DNA damage in species and chromosomal changes in mammalian cells. Phase II tests are used to confirm the results of Phase I. More expensive tests use narrower and more definitive bioassays in cultures, plants, insects, and mammals. Chemicals are tested for both mutagenicity and carcinogenicity. Phase III assesses the risk involved with a chemical. Whole-animal bioassays are used to determine quantitative hazards. Within Phases I and II a 'core battery' of tests is used to indicate a probable negative result, thus eliminating unnecessary testing. The phased approach has been used to test 38 pesticides. The results are discussed as an illustration of how the method works. (71 Refs)

37. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

Eighteen monographs present experimental and human data for the following antineoplastic and immunosuppressive agents: 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins (sulfates and hydrochlorides), chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulfan, vinblastine sulfate, and vincristine sulfate. Section 1 of each monograph summarizes chemical and physical properties; Section 2 describes production, use, occurrence, and analysis. Section 3 covers biological data relevant to evaluation of carcinogenic risk in humans, including carcinogenicity studies, toxic effects, metabolic data, mutagenicity and other short-term tests, and when available case reports or epidemiological studies of cancers present in patients treated with the compound. Section 4 summarizes pertinent animal and human data and gives critical views of the IARC Working Group. (1452 Refs)

38. THE DETECTION OF THE ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Pimentel E
Centro Nacional de Genetica Humana y Experimental (UCV - MSAS), Caracas, Venezuela
Rev Fund Jose Maria Vargas; 5(17):7-12 1981

Cancer is the public health problem, in Venezuela as in many other countries it is in the third place as the cause of death. The etiologic and pathogenic factors that could be related to the origin of cancer are endogenous (genetic, immunologic, hormonal, metabolic, actuarial, age related) or exogenous (radiation, chemical agents, viruses). More than 90% carcinogens are also mutagens, although there are notable exceptions. Generally used mutagenic Ames test, which is simple, rapid and cheap should be complemented with mammal test including human cells cultivated in vitro. With advances in technology and industrialization, old, new and more products are used and distributed throughout the world. They should be tested and monitored before disasters occur. (16 Refs) (In SPA)

39. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TES TS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. This Oncology Overview addresses itself to the development and direct application of short-term, rapid tests or assays in prokaryotic and lower eukaryotic microorganisms which screen for the carcinogenicity or mutagenicity of chemicals and other agents. This scope covers the experimental designs and specificities, modifications and improvements in methodologies and selections of test vehicles for short-term assays. In addition to reviewing the development of standard procedures, this Overview includes the development of reporting standards for mutagen and carcinogen tests. The review or evaluation of test systems is also covered. This Oncology Overview specifically excludes studies in which the use of short-term test systems appears, more or less, to be incidental to investigations of the molecular mechanism of carcinogen metabolism, activation, DNA alteration, or the binding of carcinogens to macromolecules.

40. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

Development of short-term tests for mutagenicity screening and the problems involved in their use for predicting carcinogenic hazard to humans are reviewed. Five groups of tests are described: (1) mutagenesis in microorganisms (eg Salmonella/Ames test, Escherichia coli K-12 reversion and forward mutation tests), (2) mutagenesis in mammalian cells (eg primary or early passage Syrian hamster embryo cells and cultured Chinese hamster V79 cells), (3) DNA damage/repair tests and DNA replication inhibition (eg unscheduled DNA synthesis in human skin and foreskin fibroblasts and in human Hela cells), (4) cytogenetic tests in vitro (eg chromosome aberrations in Chinese hamster cells and in cultured human lymphocytes), and (5) in vitro cell transformations (eg primary and early passage Syrian hamster embryo cells). The inability to validate mammalian bioassays or in vitro screening tests with human data complicates environmental toxicology and protection of the human environment. Acting only after a compound has been shown to be a human carcinogen is tantamount to experimenting with the human population. However, the economic consequences of over-regulation are clearly undesirable. Short-term tests by themselves do not constitute definite evidence of carcinogenic threat to humans, but positive responses are considered suggestive evidence. (90 Refs)

41. HUMAN RISK ASSESSMENT FROM ANIMAL DATA.

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ACS Symp Ser; 160:493-501 1981

The three fundamental methods of estimating potential human risk from toxic substances are epidemiological studies, animal tests, and short-term or in vitro tests. Epidemiology lack sensitivity, making assessments difficult. Mammalian surrogates are used in laboratory research, because they are anatomically, physiologically, and biochemically similar, have similar health and disease manifestations and causes, and respond similarly to exogenous agents. However, the extrapolation of animal toxicity data to humans is based on unproven assumptions. Factors that should be considered in evaluating a possible hazardous substance are (1) the validity of animal data, (2) the wt of toxicological evidence, (3) the characteristics of the test substance, and (4) the quantitative risk assessment. Evaluation of test data should allow for the possibility of different responses to chemicals among species, the existence of threshold doses, and differences in sensitivity between humans and test animals. Proper education is urged to aid public understanding of current risk assessments. (no Refs)

42. MUTAGENESIS IN MAMMALIAN CELLS.

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Mutat Res; 86(3):307-327 1981

This study examines characteristics of the mammalian cells in culture in relation to their use in chemical mutagenesis study. Carcinogenic transformation of animal cells might be due to the induction of several mutations that enabled the affected cell to overcome the normal controls of cell division. Criteria for recognizing transformation to malignancy in cultured cells vary between different cell systems. The transformation appears to be a multistep process. The role of mutagenesis in malignant transformation will be better understood when the underlying mechanisms of cellular differentiation are elucidated. Mutagenesis and even more so carcinogenesis are very complex processes. (145 Refs)

43. THE INCREASED ROLE OF CHEMISTRY IN TOXICOLOGY.

Cairns T

Dept Health and Human Services, Natl. Center for Toxicological Res., Food and Drug Administration, Jefferson, AR, 72079

ACS Symp Ser; 160:335-347 1981

At present the principle sources of evidence for identification of carcinogens a re human epidemiological evidence, long-term bioassays in animals, and short-term tests that suggest carcinogenic activity. In vivo studies have been criticized for their dose levels and reliability. More emphasis on the chemical discipline is urged in the investigation of the biochemical mechanisms of carcinogenesis. (8 Refs)

44. SISTER CHROMATID EXCHANGES IN PERIPHERAL LYMPHOCYTES AFTER PREOPERATIVE MAMMOGRAPHY.

Husum B, Wulf HC, Niebuhr E

Dept. Anesthesia, Gentofte Hosp., DK-2900 Hellerup, Denmark

Radiat Res; 87(3):684-688 1981

The sister chromatid exchange (SCE) rates were studied in the in peripheral lymphocytes of 64 breast cancer patients (17-82 yr old) who had been investigated preoperatively with mammography and in 64 patients (17-82 yr old) without preoperative mammography. The two groups of patients were identical with respect to age, smoking habits, and incidence of malignant breast tumors. Multiple regression analysis of the rate of SCE indicated that preoperative mammography did not influence the SCE rate, nor did patient age or the tumor character. A statistically significant correlation could be demonstrated between SCE and cigarette consumption ($r = 0.48$, $n = 131$, P less than 0.001). The results confirm in vitro studies indicating the SCE test system is not useful for evaluation of in vivo exposure to low levels of ionizing radiation. (13 Refs)

45. OCCUPATIONALLY RELATED CANCER.

Howard JK
No affiliation given
Practitioner; 225(1356):810,812,814-815,817 1981

While the existence of an 'epidemic of cancer' attributable largely to exposure to chemicals from industrial processes is not supported by the evidence (both age-standardized incidence and mortality for all forms of cancer are beginning to fall), occupational cancer remains of considerable importance because, at least in principle, it is the most preventable form of cancer. In the past isolated observations have been used to implicate an etiological agent (scrotal cancer in chimney sweeps); the assessment of carcinogenic potential of workplace materials must, however, be placed on a more secure basis. Three tools which may be used to identify the carcinogenic potential of an industrial process or material are human epidemiology, animal tests, and short-term predictive tests. Problems associated with human epidemiological studies include long latent period, lack of specificity, and lack of follow-up in older workers and destruction of their records. While at present great reliance is placed upon animal studies, serious shortcomings include differences in metabolic processes in different species and differences due to strain and route of administration. Short-term predictive tests, such as the Ames test, only indicate a mutagen in a particular bacterial system, but there is fairly good correlation when these systems are tested with known ca rcinogens and non-carcinogens. Problems of dealing with potential carcinogenic agents under present conditions are discussed. Advocacy of a 'no carcinogens in the workplace' policy is recognized as unrealistic. The importance of occupational history for all patients with cancer, and indeed for all patients, is stressed. (9 Refs)

46. THE ROLE OF HUMAN GENETIC MONITORING IN THE WORKPLACE.

Dabney BJ
IBM Corporation, P.O. Box 1900, Boulder, CO, 80302
JOM; 23(9):626-631 1981

The history and current state of some newer short-term tests for occupational genetic monitoring are reviewed. These are: cytogenetics, sister chromatid exchange, body fluid analysis, tests utilizing sperm, and detection of somatic cell variants. Occupational studies on benzene, vinyl chloride monomer, and epichlorohydrin are critically discussed from the standpoints of design and interpretation. It is concluded that these tests are not appropriate for risk assessment at the present time. Their clinical relevance, if any, is unknown. Proper validation and standardization have not been done, and design problems have often clouded the results of previous studies. There is a critical need for further research in the area of occupational genetic monitoring. Future applications should include integration with prospective morbidity and mortality studies, standardization of design and statistical methods, and development of new tests with genetically relevant endpoints. (Author abstract) (44 Refs)

47. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

Bigger CA, Dipple A, Tomaszewski JE, Lake RS
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from those generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.

Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
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10. PANCREATIC CANCER.

Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.

Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).

Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
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15. LIFESTYLE AND CANCER.

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International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.

Zamfir G, Diaconu R
Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.

Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001;; OB-81/01:95pp. 1981

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ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

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24. BURKITT'S LYMPHOMA.

Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

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Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903;; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.

Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Saint Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

SERIES CK19 No. 82/02

FEBRUARY, 1982

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IN VIVO MAMMALIAN SHORT-TERM TESTS

1. ANALYSIS OF MUTAGENIC ACTIVITY OF NITROFURYLACRYLIC ACID.

Zhurkov VS, Shram RIa
A. N. Sysin Inst. General and Commune Hygiene, Moscow, USSR
Vopr Pitan; (4):63-67 1981

The potential mutagenic activity of sodium salt of 3-(5-nitro-2-furyl)acrylic acid (5-NFA) currently used as a wine stabilizer

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

was tested in random-bred ICR-SPF mice. Single or repeated 5-NFA administration (intragastrically or with drinking water) did not induce dominant lethals, chromosome aberrations, or point mutations. (13 Refs) (In RUS)

BACTERIAL TEST SYSTEMS: SALMONELLA

2. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs. The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, reduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

3. COMPARISON OF THE MUTAGENICITY OF THE DIET IN RELATION TO MORTALITY FROM GASTRIC CANCER. II. MUTAGENICITY OF THE FOODS INGESTED BY THE INHABITANTS OF THE COUNTRYSIDE OF NARA AND KAGOSHIMA (MEETING ABSTRACT).

Michioka I, Kamiyama S
Dept. Hygiene, Akita Univ., Sch. Medicine, Hondo, Akita 010, Japan
Nippon Eiseigaku Zasshi; 36(1):178 1981

Foods to be consumed by the inhabitants of the villages in Haibara-machi, Nara Prefecture, and Togo-cho, Kagoshima Prefecture, which have different mortalities from gastric cancer, were frozen and air-mailed to this facility where they were thawed and the mutagenicity of the acetone-soluble fraction of the ether:petroleum ether (1:1) extract of the homogenate of the edible part was determined by the Ames' method with Salmonella typhimurium TA100. The foods with a relative mutagenicity rate of less than 1.5, 1.5-3.0 and more than 3.0 in the extract were designated negative, false-positive and positive, respectively. The rate of ingestion of negative and positive foods was strongly related to the mutagenicity of the foods for Akita and Iwate. However, in Nara the positive mutagenicity rate was low compared to that of gastric cancer mortality, which was high. The presence of some factors which promote the action of the mutagenic substances in foods on the gastric epithelium was thought to be responsible for the incidence of gastric cancer in Nara. (no Refs) (In JPN)

4. THE CHEMICAL AND BIOCHEMICAL CHARACTERIZATION OF PARTICULATE MATTER AS PART OF AN EPIDEMIOLOGICAL CANCER STUDY.

Wesolowski JJ, Flessel CP, Twiss S, Cheng J, Chan R, Garcia L, Ondo J, Fong A, Lum S

Air and Industrial Hygiene Lab., California Dept. Health Services, Berkeley, CA, 94704

J Aerosol Sci; 12(3):208-212 1981

During the winter season (November-February) 6-day high-vol glass filters were composited from each of 15 stations in Contra Costa County, California. Particulate matter was analyzed for total suspended particulate, benzene soluble organics (BSO), SO4, NO3, Pb, selected polycyclic aromatic hydrocarbons (PAH), and mutagenic activity. The five PAH, benzo(a)pyrene, benzo(ghi)perylene, benz(a)anthracene, chrysene, and coronene [a possible tracer for vehicle emissions], were quantitated by UV absorption an fluorescence. Mutagenicity was determined using the Ames test, with and without rat liver fraction S9. Since the correlation coefficients (Spearman) between mutagenicity (+S9) values and concentrations of the various PAH were only 0.33, 0.41, 0.36, 0.31 and 0.51, respectively, it is concluded that quantitation of the five PAH is not a good measure of air mutagenicity, which is consistent with the fact that these PAH constitute only about 2% of total air mutagenicity. Contour maps showing variations in air pollution will be useful for comparison of cancer incidence. The monitoring stations do provide some data on sources of pollution. High correlations between Pb, BSO and the five PAH implicate vehicles as a source. However, low correlations between mutagenicity (with or without S9) and these factors indicate mutagenicity may also derive from other sources. (12 Refs)

5. A POTENT MUTAGEN IN BROILED FISH. PART 1. 2-AMINO-3-METHYL-3H-IMIDAZO[4,5-F]QUINOLINE.

Kasai H, Yamaizumi Z, Nishimura S, Wakabayashi K, Nagao M, Sugimura T, Spingarn NE, Weisburger JH, Yokoyama S, Miyazawa T

Biology Div., Natl. Cancer Center Res. Inst., Chuo-ku, Tokyo, Japan

J Chem Soc [Perkin I]; (8):2290-2293 1981

Sun-dried sardines were broiled in normal fashion, ground, and extracted with methanol. The residue showed strong mutagenicity in Salmonella typhimurium strain TA98 in the presence of S-9 mixture, according to the Ames method. After further fractionation a neutral fraction was obtained that retained 40% of the mutagenicity of the original fraction. Purification yielded a mutagenic compound . The compound was identified by nuclear magnetic resonance spectrum and high- and low-resolution mass spectra as 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (AMIQ). The identification was confirmed by synthesis of the compound. The structure is a six-six-five-membered ring. The mutagenicity of AMIQ was much higher than that of other mutagens isolated from protein pyrolysis products. The cause of the high mutagenicity is as yet unknown. (32 Refs)

6. THE MUTAGENIC EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM II AND ITS DEGRADATION PRODUCTS IN THE AMES MICROBIAL ASSAY.

Peer RL, Litz DA
(c/o Litz) Toxicology Dept., Bristol Laboratories, Syracuse, NY, 13201
Environ Mutagen; 3(5):555-563 1981

The Ames microbial mutagenicity assay was used to test the mutagenicity of cis-diamminedichloroplatinum (II) (cis-DDP) and its degradation products (obtained from a soln aged for 12 mo at 37 C), platin B salt, magnus red, and magnus red anion salt in order to determine if the positive mutagenic response of the platinum compound could be due to, or enhanced by, the presence of degradation products. A significant increase in hist+-revertants occurred with Salmonella strains TA98, TA100, TA92, and TA94 with platin B salt, magnus red, magnus red anion salt, and lyophilized cis-DDP. The aged cisplatin, however, exhibited an increase only with strains TA100, TA92, and TA94. All degradation products exhibited a slight but significant mutagenic effect with strains TA1535 and TA1537. The mixed function oxidase activation system was required for mutagenicity only in the positive control ethidium bromide. These results indicate that platinum degradation complexes are weak mutagens which can induce both base pair and frameshift-type mutations. (32 Refs)

7. MUTAGENICITY OF ISOMERIC BETA, GAMMA, GAMMA-UNSATURATED N-NITROSAMINES DERIVED FROM TERPENE ALKANOLAMINES.

Abidi SL, Finch RA
P. O. Box 65, La Crosse, WI, 54601
Environ Mutagen; 3(5):587-591 1981

The Ames Salmonella/microsome mutagenicity test was performed on a 1:2 mixture of cis-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (cis-NDOA) and trans-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (trans-NDOA). With the cis,trans-NDOA mixture, tested at dose levels of 50, 100, and 250 ug/incubation mixture (IM), without S-9 activation, no significant increase in the number of revertant colonies/plate was seen in any of the tester strains and no dose-response relationship was noted. At doses of 50o and 100 ug/IM in the presence of S-9 activation, significantly greater numbers of revertant colonies were noted only in tester strains TA100 and TA1535. A cytotoxic effect was noted in all the tester strains at a dose level of 250 ug/IM. A slight cytotoxic effect was noted in strain TA1535 at a dose level of 100 ug/IM. It was concluded that under the cond itions of the test, the mixture of cis and trans isomers of NDOA is mutagenic for the Salmonella tester strains TA100 and TA1535 in the presence of Aroclor 1254-induced rat liver S-9 activation system. (6 Refs)

8. MUTAGENICITY OF THE REACTION PRODUCTS OF L-ASCORBIC ACID AND L-TRYPTOPHAN.

Kanamori H, Morimoto K, Kinae N, Tomita I
Hiroshima Prefectural Institute of Public Health, Uzina-Kanda, Hiroshima 734, Japan
Yakugaku Zasshi; 101(7):596-604 1981

Glycine, dl-phenylalanine, l-tryptophan, and ammonia were allowed to react with l-ascorbic acid and d-glucose, in a 0.1M phosphate buffer (pH 7.0) at 37 C for 2 mo; the reaction mixtures were analyzed structurally and were tested for mutagenicity to Salmonella typhimurium TA 98 and TA 100 Ames test and to Bacillus subtilis. Except for the mixture of l-ascorbic acid and ammonia, DNA-damaging effects were seen for reaction mixtures of l-ascorbic acid, but none were observed for reaction mixtures of d-glucose. Reaction mixtures of l-tryptophan and l-ascorbic acid were found to be DNA-damaging at day 8 after mixing, and the activity of the reaction mixture increased by mo 2, but DNA-damaging activity of this reaction mixture decreased after 2 mo. Following extraction of the reaction products of l-tryptophan and l-ascorbic acid with benzene and ethyl acetate and purification with silica-gel column chromatography and thin layer chromatography, mutagenic activity against S typhimurium TA 100 was observed for one fraction containing 1-(2-furyl)-9H-pyrido-[3,4-b]-indole with or without S-9 mixture and for 1-(2-furyl)-9H-pyrido[3,4-b]-indole carboxylic acid in the absence of the S-9 mixture. (15 Refs) (In JPN)

9. INFLUENCE OF MICROSOMAL AND CYTOSOLIC FRACTIONS FROM RAT, MOUSE, AND HAMSTER LIVER ON THE MUTAGENICITY OF DIMETHYLNITROSAMINE IN THE SALMONELLA PLATE INCORPORATION ASSAY.

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Genetic Toxicology Branch, Dept. Health and Human Services, Food and Drug Admin., Washington, DC, 20204
Cancer Res; 41(11,part1):4361-4367 1981

Dimethylnitrosamine (DMN) was mutagenic in the Salmonella plate incorporation assay (Ames test) at a level of 10 umol/plate (3.7 mM) in the presence of hamster liver S-9. Mutagenicity of DMN at this level was not observed when the S-9 was derived from mouse or rat liver, although the mouse liver and hamster liver S-9 had similar DMN demethylase activities. Both mouse and rat liver S-9 inhibited the mutagenicity of DMN mediated by hamster liver S-9; the inhibitory factor was contained in the microsomal fraction. Mouse or rat liver microsomes did not inhibit the DMN demethylase activity of hamster liver S-9. The microsomal inhibitor from rat or mouse liver was stable at 60 but was inactivated at 70 C. DMN demethylase from both rat and mouse liver was inactivated at 60 C. Although the DMN demethylase activity of hamster liver S-9 was contained in the microsomal fraction, DMN mutagenesis under conditions of the assay required the presence of both microsomal and cytosolic (S-105) fractions; the cytosols from hamsters, mice, and rats were all effective. The cytosolic factor required for DMN mutagenesis was sensitive to trypsin and was not dialyzable. The presence of an inhibitor of DMN activation in rat and mouse microsomes may account for, or contribute to, the failure of liver S-9 preparations from these species to activate DMN to a mutagen under standard conditions of the Ames test. The requirement for the cytosolic fraction may indicate that DMN demethylase is not sufficient for the activation of DMN to a mutagen under the conditions used in these studies. (Author abstract) (46 Refs)

10. EXPOSURE TO CARCINOGENIC CHEMICALS AND SMOKING INCREASES URINARY EXCRETION OF MUTAGENS IN HUMANS.

Dolara P, Mazzoli S, Rosi D, Buiatti E, Baccetti S, Turchi A, Vannucci V
Istituto di Farmacologia e Tossicologia, Viale Morgagni 65, Florence, Italy
J Toxicol Environ Health; 8(1/2):95-103 1981

The Salmonella/microsome test was employed to test for mutagenic chemicals in 24-hr urine samples in male unexposed controls and workers in two chemical plants. Workers in one plant were exposed to solvents and dyes, in the other to pharmaceutical compounds; operations were carried out in open manner. Both groups ranged in age from 25-50 yr, mean for controls was 36, for workers 41. A baseline for mutagenic activity was determined by dose response curves obtained by plating variable vol of the urine of smoking controls. With tester strain TA1538, urine of nonsmoking chemical workers showed higher mutagenic activity than that of controls with in vivo metabolic activation. Urine of smoking controls and smoking workers showed no difference. There was a difference between smoking and nonsmoking controls. With tester strain TA100 the urine of both smoking and nonsmoking workers showed greater mutagenic activity than controls. When the urines of 10 nonsmoking workers with positive mutagenic activity were tested 20 days after a leave, mutagenicity in some individuals was reduced. Although the practice of smoking produced some difficulties, the results indicate the usefulness of the Salmonella/microsome mutagenicity test in human urine. (9 Refs)

11. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

12. ANALYTICAL AND BIOLOGICAL ANALYSES OF TEST MATERIALS FROM THE SYNTHETIC FUEL TECHNOLOGIES. IV. STUDIES OF CHEMICAL STRUCTURE-MUTAGENIC ACTIVITY RELATIONSHIPS OF AROMATIC NITROGEN COMPOUNDS RELEVANT TO SYNFUELS.

Ho CH, Clark BR, Guerin MR, Barkenbus BD, Rao TK, Epler JL
Analytical Chemistry Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 85(5):335-345 1981

Mutagenicity of model compounds of aromatic nitrogen compound classes found in or possibly present in synfuel products was studied. Salmonella typhimurium tester strains TA1535, TA1537, TA1538, TA98, and TA100 were employed. Aromatic hydrocarbons with 1-4 rings produced no mutagenicity but 5-ring compounds (such as perylene and benzo(a)pyrene) exhibited significant mutagenicity. Most N-heterocyclics of from 1-4 rings produced no mutagenicity; 5-ring members like 1,2,7,8-dibenzacridine and 10-azobenzo(a)pyrene showed high activities while 2,2'-bipyridine and quinoline showed only slight activities. Presence of nitrogen may increase mutagenicity slightly but is not as important as the number of fused rings. Effects of amino and nitro groups substituted on the aromatic ring and of compounds containing 1 N atom in the ring and 1 amino substituent are also presented. Amino substituents have a significant effect in N-heterocyclic parent compounds. Multi-ring aromatic amines give a definite activity for a particular isomer whether the amino functional group is primary, secondary, or tertiary. Observed trends are discussed with reference to molecular structural features. (16 Refs)

13. CARCINOGEN BIOASSAY AND MUTAGENICITY STUDIES WITH THE HYPOLIPIDEMIC AGENT GEMFIBROZIL.

Fitzgerald JE, Sanyer JL, Schardein JL, Lake RS, McGuire EJ, De la Iglesia FA
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JNCI; 67(5):1105-1116 1981

Gemfibrozil, a novel hypolipidemic agent identified chemically as 2,2-dimethyl-5 -(2,5-xylyloxy)valeric acid, was evaluated for mutagenic potential in in vitro assays with Salmonella typhimurium. For evaluation of tumorigenic potential, gemfibrozil was administered in the diet (0, 30, and 300 mg gemfibrozil/kg) to groups of noninbred CD-1 mice (72/sex) and noninbred CD rats (50/sex) for 78 and 104 wk, respectively. In the bacterial mutagenesis assays, between 100 and 2,500 ug gemfibrozil/plate failed to induce a significant increase in revertant bacterial colonies. Neither was a mutagenic response in bacterial assays induced at concentrations up to 300 ug of five in vivo metabolites of gemfibrozil isolated from rat urine/plate. In mice, gemfibrozil did not significantly increase the frequency or the mean latency period of tumors. In rats, the statistically significant increases in hepatocellular tumors and interstitial cell tumors of the testes were dose related. Adrenal medullary and pancreatic acinar tumors were increased in male rats but were inversely dose related. Under the conditions of this assay, gemfibrozil did not elicit a tumorigenic potential in mice and female rats. In male rats and related to the hepatocellular tumor response, the peroxisome proliferation seen did not occur in humans chronically administered hypolipidemics. (Author abstract) (22 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: MUTAGENICITY

14. THE THYMIDINE INCORPORATION INHIBITING SCREENING SYSTEM (TTS) TO TEST CARCINOGENIC SUBSTANCES (A NUCLEAR DNA SYNTHESIS SUPPRESSIVE SHORT TERM TEST).

Amlacher E, Rudolph C
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Arch Geschwulstforsch; 51(7):605-610 1981

A short-term screening test is described in which the effects of carcinogens on DNA synthesis were measured by the determination of the mean number of silver grains per nucleus in the renal tubule and liver epithelia of 14-day-old CBA mice following ip injection of carcinogen. Fifteen hr after the injection of 0.1 ml of the dissolved chemical in a concentration representing 15/30% of the LD50, 3H-thymidine was injected ip. Autoradiographs of the nuclei of the renal tubular epithelia and of the liver epithelium were examined by visual silver grain counting. From this test, it was demonstrated that carcinogenic compounds of several different chemical classes (nitrosated amines, azo dyes, azo compounds, aliphatic iso- and heterocycles, aromatic amines, and metallic ions) partially inhibited the nuclear incorporation of thymidine in a significant manner over a time period longer than 24 hr. This decrease was expressed as a decrease of the mean of the silver grain number per nucleus in comparison with unaltered controls. This decrease was used as a criterion for the suppressive effect of carcinogenic substances on the rate of nuclear DNA synthesis. No false-positive results were obtained for noncarcinogenic compounds. The effectiveness of this test is discussed. (6 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: CYTOGENETIC TESTS

15. SISTER CHROMATID EXCHANGE INDUCED BY ANTI-HERPES DRUGS.

Cassiman JJ, De Clercq E, Jones AS, Walker RT, Van der Berghe H
Div. Human Genetics, Univ. Leuven, B-3000 Leuven, Belgium
Br Med J; 283(6295):817-818 1981

The rate of sister chromatid exchange induced by several anti-herpes agents was measured to assess their potential mutagenicity. The agents 5-iodo-deoxyuridine (IDU), 5-trifluoromethyl-deoxyuridine (TFT), and [E]-5-(2-bromovinyl)-deoxyuridine (BVDU)-were incubated at various concentrations with human lymphocytes and fibroblasts, and the rate of sister chromatid exchanges was measured. In lymphocytes and fibroblasts BVDU and IDU did not induce exchange except at concentrations of 50 mg/l, while TFT increased the rate of exchange at a concentration of 0.5 mg/l. The rate of sister chromatid exchange is a sensitive index of chromosomal damage, and these findings provide information on the safety of some of the anti-herpes agents tested. TFT increased the rate of exchange at a concentration that coincides with its minimal anti-viral concentration, but BVDU did not induce exchange at therapeutic concentrations. (Author abstract) (5 Refs)

16. POTENCY OF SOME CARBAMATES AS MULTIPLE TISSUE SISTER CHROMATID EXCHANGE INDUCERS AND COMPARISON WITH KNOWN CARCINOGENIC ACTIVITIES.

Cheng M, Conner MK, Alarie Y
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Cancer Res; 41(11,part1):4489-4492 1981

The ethyl, ethyl N-hydroxy, isopropyl, and methyl esters of carbamic acid were examined for their abilities to induce sister chromatid exchanges (SCEs) in alveolar macrophages, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. The relative potencies in inducing SCE, ethyl greater than ethyl N-hydroxy- greater than isopropyl, paralleled previously described activities for induction of lung adenomas in strain A mice. The noncarcinogenic methyl carbamate was inactive in the SCE assay. Relative to bone marrow, regenerating liver and alveolar macrophage cells demonstrated increased susceptibility to carbamate-induced SCE. Of all carbamates studied, only the directly active compound, ethyl N-hydroxycarbamate, produced distinctly different responses in extrahepatic tissues of hepatectomized and intact mice. In intact mice, SCE levels induced by ethyl carbamate in bone marrow and alveolar macrophage cells were not significantly different whether assay followed the last of 12 (3x weekly) serial injections of 2.2 mmol/kg each or after a single injection of 2.2 mmol/kg. Linear regression relationships of log ethyl carbamate versus log SCE or log adenoma response were found to be parallel with the two assays having similar sensitivities. (Author abstract) (21 Refs)

17. EVALUATION OF EXPERIMENTAL PARAMETERS IN AN S9/HUMAN LEUKOCYTE SCE TEST WITH CYCLOPHOSPHAMIDE.

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Mutat Res; 85(5):347-356 1981

The effect of various cyclophosphamide (CP) concentrations on sister chromatid exchange (SCE) frequency and cell proliferation, and the influence of experimental parameters (S9 concentration, concentration of cofactors, and exposure time) on CP-induced effects were examined in a human WBC test. The S9 fraction was prepared from livers of Aroclor-induced male rats. S9 mix alone did not influence SCE frequency or cell proliferation. CP, 1.7 x 10(-6) to 5.0 x 10(-5) M, produced increasing delay in cell proliferation. CP-induced SCE frequencies were strongly dependent on actual S9 concentration; cell proliferation was delayed with increasing S9 concentration. Studies with different concentrations of the cofactors (NADP and glucose-6-phosphatase in a ratio of 1:2) indicated an influence on the activity of S9 mix which was not as important as S9 concentration: SCE frequency increased, but cell proliferation was slightly inhibited with prolonged exposure times. CP at 1.7 x 10(-5) M was toxic in exposures greater than 2 hr. The importance of varying experimental parameters to avoid false-negative results in microsome tests is discussed. (28 Refs)

18. SISTER CHROMATID EXCHANGE (SCE) AND STRUCTURAL CHROMOSOME ABERRATION IN MUTAGENICITY TESTING.

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Hum Genet; 58(3):235-254 1981

An objective analysis is presented of data gained so far relative to the value in mutagenicity testing of sister chromatid exchange (SCE) and classical chromosome aberration (CA) analysis. Detailed studies are reported on spontaneous SCE and chromosome damage in normal cells, and in cells of patients with genetic and neoplastic disease. Qualitative results on SCE induction and CA are presented relative to radiation, chemicals, chromosomal breakage syndromes and virus. Quantitative results are presented on potent inducers of SCE and break aberrations, substances inducing SCE but not breaks in the same test system, and clastogens with no or minor SCE-inducing activity. A section deals with modification of SCE and chromosome breakage: clastogens and anticlastogens. A discussion of molecular aspects of SCE induction and breakage involves consideration of evidence for the primary lesions leading to SCE formation, role of replication and involvement of repair mechanisms. These studies indicate SCE and structural CA are two largely different cytogenetic endpoints of mutagenic action. It is suggested that the SCE-technique is a valuable additional method for cytogenetic testing, which, however, is not adequate to replace the classical methods of analysis of structural chromosome damage. (165 Refs)

19. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.

Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

Sister chromatid exchange (SCE) as a test for mutagenic carcinogens is reviewed. Method of testing is described with respect to the genetic basis for SCE, and to cell types and animal strains for in vitro and in vivo studies. Interpretation of data is explained, including presentation (dose-response curves, data transformation, and units of expression), statistical evaluation, and criteria for negative/positive conclusions (negative agents, positive agents, provisionally positive agents). Test performance is reviewed with citations of literature, chemicals or chemical classes that give anomalous results (deoxycytidine, ascorbate, and methotrexate), chemicals or chemical classes for which the test is well suited (alkylating agents, many DNA-binding agents, certain DNA-base analogues, and agents that cause single-strand breaks), and correlation with mammalian carcinogenicity data. A protocol is suggested using in vitro and in vivo SCE analysis, and non-mammalian systems for detecting mutagens using the SCE procedure. Conclusions on the strengths and weaknesses of the assay, its role in a testing program, and recommendations for future research are presented. (169 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: TRANSFORMATION

20. TRANSFORMATION OF HAMSTER EMBRYO CELLS BY NEUTRAL STEROLS AND BILE ACIDS.

Kelsey MI, Pienta RJ
NCI, Landow Building, Room 8C25, Bethesda, MD, 20205
Toxicol Lett; 9(2):177-182 1981

Toxicity and transformation data on the neutral sterols cholesterol-alpha-epoxide and cholestan-3beta,5alpha, 6beta-triol (Triol), and on primary (cholic and chenodeoxycholic) and secondary (lithocholic and deoxycholic) bile acids are presented. Previous results showed that 10 ug/ml cholesterol is neither toxic nor cell- transforming. Cholesterol-alpha-epoxide was toxic to 50% (TD50) of cultured Syrian hamster embryo cells at 10 ug/ml, whereas TD50 for Triol occurred at a concentration 1/5 that of its precursor. In the bile acid series, the primary bile acids were less toxic than the secondary derivatives. The latter were less toxic than the oxygenated sterols. Transformation occurred at all doses tested for the oxygenated sterols. Relative cloning efficiencies compared with those found for controls at the highest doses tested were 87% and 70% for cholesterol-alpha-epoxide and Triol, respectively. The primary bile acids were toxic at 480 ug/ml (cholic acid) and 208 ug/ml (chenodeoxycholic acid), and deoxycholic acid had a cloning efficiency of 82% at the highest dose causing cell transformation. Results indicated that mammalian cell transformation may be a preferable short-term assay for structure-activity information of steroid derivatives as well as for potential carcinogenicity. (23 Refs)

ACTIVATION OF CARCINOGENS FOR SHORT-TERM TEST SYSTEMS

21. ENHANCEMENT OF N-HYDROXY-2-AMINOFLUORENE BACTERIAL MUTAGENICITY BY THE SOLUBLE PROTEIN FRACTION FROM RAT LIVER AND PARTIAL PURIFICATION OF THE ENHANCEMENT ACTIVITY.

Saccone GT, DasGupta BR, Pariza MW
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Cancer Res; 41(11,part1):4600-4605 1981

Bacterial mutagenesis from 2-aminofluorene mediated by washed rat liver microsomes was elevated 2-to 3-fold by addition of the hepatic soluble protein fraction. Enhancement was observed at 2-aminofluorene concentrations between 1 and 20 ug/assay but not at 30 to 50 ug/assay. The soluble protein fraction (without added microsomes) did not activate 2-aminofluorene for bacterial mutagenesis. However, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was enhanced by the soluble protein fraction, but only when reduced nicotinamide adenine dinucleotide phosphate was also present. On the basis of chemical assay, reduced nicotinamide adenine dinucleotide phosphate reduced 2-nitrosofluorene to N-hydroxy-2-aminofluorene and protected the hydroxylamine from oxidation, thus indicating that it was the mutagenicity of N-hydroxy-2-aminofluorene (but not 2-nitrosofluorene) which was enhanced by the soluble protein fraction. Without the added soluble protein fraction, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was unaffected by reduced nicotinamide adenine dinucleotide phosphate. We succeeded in partially purifying a protein fraction with properties of the enhancement activity. The partially purified fraction, which represents a 14-fold increase in specific activity, was assigned a mol wt of 33,500 by gel filtration through Sephadex G-100. This fraction was resolved into three components by polyacrylamide gel electrophoresis; the mol wt of the three components were determined by sodium dodecyl sulfate-polyacrylamide gel (10%) electrophoresis to be 33,000, 27,000, and 16,250. The mechanism of mutagenesis enhancement remains unknown. (Author abstract) (27 Refs)

22. RADIOSTERILIZATION OF RAT LIVER MICROSOME CONTAINING POSTMITOCHONDRIAL SUPERNATANT FOR MUTATION ASSAYS.

Barfknecht TR, Andon BM, Bishop WW, Thilly WG
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Environ Mutagen; 3(5):565-573 1981

Gamma-irradiation was tested as a method for sterilizing commercially prepared r at liver postmitochondrial supernatant (PMS) by adding a known number of radio-resistant Bacillus subtilis spores to PMS samples and determining a dose-response survival curve for the spores following gamma-irradiation. At the same time, uncontaminated samples of PMS were irradiated and assayed for their ability to metabolically activate automobile diesel soot (ADS) and soot-derived polycyclic aromatic hydrocarbons (PAH) and dimethylnitrosamine (DMN) to mutagens using the Salmonella typhimurium 8-azaguanine resistance forward mutation system. Based on the survival of B subtilis spores in frozen gamma-irradiated PMS, sterilization of PMS with a dose of 3 megarads (Mrad) was effective in reducing a contamination of 1,000 bacteria/ml or 10(6) bacteria/liter to 10(-3) bacteria/liter. At doses up to 6 Mrad at dose rates of 5 x 10(5) rads/hr there was little or no significant loss of the ability of irradiated PMS to metabolically activate ADS, and the diesel soot components, benzo(a)pyrene (BaP) and fluoranthene (FLA) to mutagens. At higher doses of gamma-irradiation, and at a dose rate of 3 x 10(6) rads/hr for 6 Mrad, a significant inactivation of the ability of PMS to activate BaP and FLA was noted. Thus, radiosterilized PMS can be used in mammalian cell mutation assay systems to detect PAH mutagenesis. (25 Refs)

23. GREATER EFFECTIVENESS OF HEPATOCYTE AND LIVER S9 PREPARATIONS FROM HAMSTERS THAN RAT PREPARATIONS IN ACTIVATING N-NITROSO COMPOUNDS TO METABOLITES MUTAGENIC TO SALMONELLA.

Raineri R, Polley JA, Andrews AW, Pienta RJ, Lijinsky W
Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
JNCI; 67(5):1117-1122 1981

A comparison was made of the ability of liver S9 and hepatocyte preparations from noninbred Syrian golden hamsters and noninbred Sprague-Dawley rats to metabolically activate a number of nitroso compounds in the Salmonella mutagenesis assay. The liver S9 and hepatocyte preparations from hamsters were consistently more effective than were preparations from rats in metabolizing nitrosodimethylamine (NDM), nitrosodiethylamine, nitrosodiallylamine, nitrosopyrrolidine (NP), nitrosomorpholine (NM), nitrosodiethylmethylurea (NDEMU), and nitrosodimethylethylurea (NDMEU) to mutagenic forms. The use of hamster S9 preparations with NP and NM resulted in up to 14x the number of revertant colonies obtained with rat preparations; in the presence of hamster hepatocytes, up to 32x the number of revertants were obtained. The S9 preparations from male hamsters not treated with the enzyme inducers phenobarbital and Aroclor 1254 were more effective than were those from female hamsters for activating NP, NM, and NDM. NDEMU and NDMEU, which have been reported to be carcinogens but not mutagens, were mutagenic in the presence of induced liver S9 or hepatocyte preparations from hamsters but not from rats. When tested with any of the S9 or hepatocyte preparations, nitrosodiphenylamine and nitrosomethylaniline, also reported to be carcinogens but not mutagens, gave no mutagenic responses. Nitrosodioctylamine, which has been reported to be noncarcinogenic, was also not mutagenic. (Author abstract) (23 Refs)

24. ACTIVATION OF CYCLOPHOSPHAMIDE USING PERFUSED RAT LIVER SYSTEM AND INDUCTION OF SISTER CHROMATID EXCHANGES IN VITRO.

Abe T, Ide T, Tosa M, Takahashi T, Takino T
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Hum Genet; 58(3):349 1981

The activation of cyclophosphamide (CPM) using perfused rat liver was studied in a simplified in vitro test system for the induction of sister chromatid exchanges (SCEs). The output fluid of CPM, perfused and recirculated in the liver of male Wistar rats, consisted of the CPM alkylating intermediate (AICPM). AICPM yielded an av 48.40 SCEs in human lymphocytes at concentrations of 10(-4) M. A clear dose relation was found between 10(-4) and 10(-6) M AICPM. (9 Refs)

25. ENZYMATIC METHYLATION OF MICROSOMAL METABOLITES OF BENZO(A)PYRENE.

Lombardi PE, Mayhew JW, Goldin BR, Gregory ME, Lynch MA, Sullivan CE, Gorbach SL
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Cancer Res; 41(11,part1):4415-4419 1981

These studies suggest that the microsomal metabolism of benzo(a)pyrene (BP) produces metabolites which can be methylated by the catechol-o-methyltransferase (COMT)/S-adenosylmethionine (SAM) enzyme/donor combination. Induced microsomes converted 12 to 15% of substrate BP to polar products. Approx 0.06% of substrate BP was recovered as COMT/SAM-reactive substances. In tests for specificity, COMT/SAM was found to react with catechols, but not with dihydrodiols, quinones, a phenol, an epoxide, or 1,4-hydroquinone. Organic extracts of COMT/[14C]SAM incubations with BP were fractionated by high-performance liquid chromatography. The appearance of radiolabeled chromatographic bands required the presence of substrate BP, microsomes, and COMT/[14C]SAM. When the Ames mutagenesis assay was supplemented with COMT/SAM, a 36% reduction was observed in the number of revertant colonies induced by the microsomal oxidation of BP. In contrast, the mutagenic properties of 2-aminofluorene were not affected by COMT/SAM. These observations indicate that COMT/SAM does not generally inhibit mixed-function oxidase activity but rather reacts with substances which are activated by ring oxygenations. (Author abstract) (33 Refs)

COMPARATIVE RESULTS FROM MULTIPLE TEST SYSTEMS

26. INDUCTION OF GENE MUTATION IN AND CELL TRANSFORMATION OF MAMMALIAN CELLS BY MODIFIED PURINES: 2-AMINOPURINE AND 6-N-HYDROXYLAMINOPURINE.

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Environmental Carcinogenesis Group, Lab. Pulmonary Function, and Toxicology Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 27709
Proc Natl Acad Sci USA; 78(9,part2):5685-5689 1981

A classical mutagen in prokaryotic systems, 2-Aminopurine is inactive as a carcinogen in two animal species. To determine the basis for this discrepancy in the correlation between carcinogenesis and mutagenesis, the ability of 2-aminopurine to induce somatic mutation and neoplastic transformation concomitantly in the same cellular system was examined. 6-N-hydroxylaminopurine, a related modified purine that is a mutagen and a carcinogen, was also studied. 2-Aminopurine was a mutagen in Syrian hamster embryo cells, but its activity was very weak. The max induced mutation frequency with either of two mutational markers was only 7 x 10(-6) mutants per surviving cell. 2-Aminopurine also induced morphological transformation of the cells under the same conditions, but the frequency was only approx 0.04% per surviving colony. Neoplastic transformation of the cells after 2-aminopurine treatment was not observed in these experiments. These results indicate that 2-aminopurine is, at best, a weak transforming agent. The lack of carcinogenic activity in vivo with 2-aminopurine is consistent with these observations. In contrast to the results with 2-aminopurine, 6-N-hydroxylaminopurine was very effective mutagen in these cells (up to 10(-3) mutants per survivor) and induced morphological transformation of the cells in a dose-dependent manner. Furthermore, neoplastic transformation was induced by this nucleic acid base analog, the correlation of mutagenic activity with transforming ability of these two modified purines supports a relationship between mutagenesis and carcinogenesis. However, relative to other carcinogens, there is a quantitative difference in the ability of 6-N-hydroxylaminopurine to induce cell transformation and mutation. For example, in benzo[a]pyrene-treated cultures, the ratio of the frequency of induced morphological transformation to that of somatic mutation was approx 100, whereas for 6-N-hydroxylaminopurine-treated cultures, the ratio of transformation to mutation was only 3-12.5. This indicates that 6-N-hydroxylaminopurine is less potent than benzo[a]pyrene in inducing transformation when compared at equal mutagenic potency. This is consistent with our hypothesis that cell transformation, and possibly cancer, occurs predominantly as the result of a mutation at the chromosome level rather than a gene mutation. (Author abstract) (27 Refs)

27. MUTAGENICITY, TUMORIGENICITY, AND ELECTROPHILIC REACTIVITY OF THE STEREOISOMERIC PLATINUM(II) COMPLEXES OF 1,2-DIAMINOCYCLOHEXANE.

Leopold WR, Batzinger RP, Miller EC, Miller JA, Earhart RH
(c/o Miller) McArdle Lab. Cancer Res., Univ. Wisconsin Center for Health Sciences, Madison, WI, 53706
Cancer Res; 41(11,part1):4368-4377 1981

Without external activation, cis- and trans-dichlorodiammineplatinum(II) and the cis, trans(-), and trans(+) forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) showed a 400-fold range of mutagenicity for Salmonella typhimurium TA100 and TA98; they were 2 to 10x more mutagenic for strain TA100 than for strain TA98. With strain TA100, trans-DDP was less than 0.5% as mutagenic as the cis isomer, which produced 180 revertants/nmol. For the diaminocyclohexane complexes, mutagenic activity was strongly dependent on the stereoisomer of the diaminocyclohexane in the complex. Thus, with strain TA100, the trans(+) forms of DDCP and SHP produced 220 and 66 revertants/nmol, respectively, while the cis- and trans(-) isomers induced only 10 and 5% as many revertants as the trans(+) forms. The SHP complexes were the most reactive toward DNA and produced a greater reduction in the transforming activity of Bacillus subtilis DNA after 3-hr reaction times than did the DDP or DDCP complexes. With 20-hr reaction times, all of the platinum complexes showed similar extents of reaction with DNA and caused approx equal losses of transforming activity. The stereoisomeric form of the diaminocyclohexane ligand of the DDCP or SHP complexes did not affect either the reactivity of the complex with DNA or its ability to reduce the transforming activity of DNA. Significant increases in the number of lung adenomas in A/J mice were induced by multiple ip injections of cis-DDP and each of the DDCP and SHP complexes (total doses, 21 to 108 umol/kg body wt). Similar treatments with cis-DDP caused a significant increase in the number of skin papillomas in female CD-1 mice given promoting treatments with croton oil; the DDCP and SHP complexes had little or no activity in this system. At these levels, trans-DDP was not active for the induction of either lung adenomas or skin tumors. With the systems used for this study, the mutagenicities and tumorigenicities of the platinum(II) complexes did not correlate with their reported antitumor activities. Further studies appear warranted to determine whether there may be effective antitumor platinum (II) complexes that are not strongly mutagenic or carcinogenic. (Author abstract) (56 Refs)

28. MUTAGENICITY OF MUNICIPAL WATER OBTAINED FROM AN AGRICULTURAL AREA.

Heartlein MW, DeMarini DM, Katz AJ, Means JC, Plewa MJ, Brockman HE

(c/o Brockman) Dept. Biological Sciences, Illinois State Univ., Normal, IL, 61761

Environ Mutagen; 3(5):519-530 1981

The lake water from Lake Bloomington, Illinois, and the tap water made from it were tested for mutagenicity in the Salmonella/microsome test, samples of unconcentrated water were tested in the waxy-90 reverse-mutation tests in Zea mays, and analytical studies involving gas chromatography and mass spectroscopy were combined with the mutation studies to determine which chemicals were present in the water samples. Samples were collected monthly from May to October 1979 and concentrated 3,000x with XAD-2 resin. The drinking water was mutagenic in the Salmonella/microsome test, with the May water concentrate being 60x more mutagenic than the other concentrates in TA100 in the presence of S-9 mix. Many of the concentrates were toxic to bacteria in the absence of S-9 mix. A number of organic contaminants were found by chemical analysis that were absent from control concentrates prepared from deionized and distilled treated well water. No mutagenicity was detected in the reverse mutation test with unconcentrated lake and tap water. Thus, contamination of drinking water with agricultural and/or industrial chemicals may result in a potential health hazard. (37 Refs)

EVALUATIONS, REVIEWS AND OTHER RELATED STUDIES

29. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.

Lewis BB, Chestner SB

800-A Fifth Ave., Suite 503, New York, NY, 10021

J Am Dent Assoc; 103(3):429-434 1981

A review of the carcinogenic and mutagenic potential of formaldehyde products used in dentistry is presented. Dentists performing endodontic therapy may use formocresol and formaldehyde paste. Tissue contact results either directly or by contact with the gaseous formaldehyde phase. While various short-term tests have indicated the mutagenicity of formaldehyde, they are not conclusive for the mammalian species. Clinical studies involving chronic topical application of formalin have demonstrated the induction of leukoplakia and lesions resembling carcinoma in situ. The respiratory tract may be the area for the greatest risk of the development of tumors. Animal studies demonstrate that formaldehyde may affect reproduction potential. Formaldehyde should be considered a potential carcinogen in humans. Formaldehyde poses problems to systemic health via ingestion routes, interaction in air with other aldehydes, and in final breakdown products of formalin in the body. If formaldehyde is clearly not necessary, why is it used at all, particularly in light of its deleterious effects. (115 Refs)

30. CARCINOGENICITY, MUTAGENICITY AND TERATOGENICITY OF NICKEL.

Leonard A, Gerber GB, Jacquet P
Dept. Radiation Biology, C.E.N.-S.C.K., B-2400 Mol, Belgium
Mutat Res; 87(1):1-15 1981

Nickel is widely used in the metallurgical industry. It is not released into the environment in large quantities, but poses an occupational hazard to human health. Ingested nickel is not readily absorbed, hence it is relatively nontoxic. Inhaled nickel is toxic in certain forms. Nickel carb onyl at 30 ppm for 30 min is lethal. Half-life in the body is less than 1 wk. Metallic nickel can cause sensitization of the immune system. Nickel compounds are carcinogenic in inverse proportion to their solubility in aqueous media. Nickel sulfide appears to have the greatest carcinogenicity. The lungs and nasal tissue are favored sites of nickel-induced cancers. Tumor types induced include undifferentiated sarcoma, fibrosarcoma, carcinoma, leukemia, and lymphoma. The mutagenicity of nickel is uncertain: nickel may be mutagenic in mammals but not in microorganisms. It is capable of crossing the placenta and has teratogenic effects, including fetal mortality, exencephaly, and cystic lung disease, in some species. Effects may be delayed by retarded transfer across the placenta. (129 Refs)

31. CHEMICAL COMPOUNDS AND CANCER RISK.

Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981

Recent research on the cancer risk of chemical compounds is reviewed. Cancer risk is strongly influenced by environmental factors, which is evidenced by the great stability of so-called cancer patterns within certain populations, by greatly stable differences between the cancer patterns of differents populations, and by changes in the cancer pattern within immigrant and emigrant populations. It has not yet been possible to establish causal relationships with exactly definable risk factors for about half of all neoplasms in men and about 3/4 of all neoplasms in women. It is unjustified scientifically to distinguish between animal and human carcinogens. Chemical substances found to be carcinogenic in animal experiments should be considered as potential carcinogens in humans as well. Dose-effect relationships have been proved for chemical carcinogens but the existence of threshold doses has not yet been elucidated. Short-term screening tests are of great value in the detection of carcinogenic effects of chemical substances, even though they are unable to replace long-term animal experiments and epidemiological surveys. (22 Refs) (In GER)

32. A STUDY OF THE MUTAGENIC PROPERTIES OF CHEMICAL PRODUCTS.

Archimbaud M, Chalabreysse J, Penalva JM, Bourgineau G
Departement de Protection, Service d'Hygiene Industrielle, Institut de Protection Nucleaire, Pierrelatte 26, France
Inf Chim; (214):217-219 1981

The use of the Ames mutagenicity test for the determination of the mutagenic potential of industrial products and of the components released into the atmosphere during their use is discussed in relation to the law on control of chemical products (July 12, 1977). According to this law two short-term tests, one which is bacteriological in nature, should be performed on chemical products. The process of mutagenicity and the Ames test itself are described. (6 Refs) (In FRE)

33. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.

Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981

Recent studies on the hygienic effects of phenoxy acids used as pesticides are reviewed. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin, occurring in a small amount as impurity in (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), was found to be a carcinogen and possibly a promotor in experimental animals. Small quantities of other dioxins, eg, tetrachloro-p-dioxin, were found in (2,4-dichlorophenoxy)acetic acid (2,4-D). Increased incidence of tumors and malformations due to 2,4,5-T was found in mice, and increased incidence of lymphosarcoma and tumors of endocrine organs was found in rats treated with 2,4-D. The mutagenicity tests of the phenoxy acids and dioxins yielded contradictory results. No carcinogenic effect of 2,4-D and 2,4,5-T was demonstrated in some animal experiments. Epidemiological studies showed a link between soft-tissue sarcoma and lymphosarcoma and exposure to phenoxy acids. Other epidemiological studies showed no relationship. Yet, a link between cancer and exposure to 2,4,5-T seems to exist in the light of experimental and epidemiological data. (10 Refs) (In SWE)

34. CARCINOGEN TESTING: CURRENT PROBLEMS AND NEW APPROACHES.

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY, 10595
Science; 214(4519):401-407 1981

The classic procedures for testing potential carcinogens in animals have basically not changed in the past 50 yr. Considerable knowledge of the mechanisms of carcinogenesis has accrued in the last 20 yr, particularly concepts on the metabolic activation of chemicals to reactive electrophilic compounds that can interact with nucleophilic cell components including DNA. These developments, in turn, have yielded a framework for integrating into carcinogen testing the determination of genetic effects of chemicals. A systematic decision point approach to carcinogen testing has been developed which entails a sequential decision-making process as specific tests are performed and evaluated prior to initiation of higher order, more complex tests. Compared to conventional bioassays in rodents, this approach provides knowledge based on mechanisms of carcinogenesis, yields a substantial amount of data at minimal cost, and forms a solid base for eventual health risk assessment. (Author abstract) (34 Refs)

35. IN VITRO MODELS AND METHODS FOR BIOASSAY AND STUDIES OF CELLULAR MECHANISMS.

Belman S, Casto B, Flessel CP, Lane BP, Loeb L, Rossman T, Sirover MA, Vainio H, Whiting R, Zakour R
New York Univ. Medical Center, New York, NY, 10016
Environ Health Perspect; 40:35-42 1981

The use of in vitro systems to detect metal carcinogens and study the mechanisms of carcinogenesis is discussed. These systems include mutagenesis in bacterial and mammalian cells, in vitro transformation, cell-free systems, chromosome aberrations, sister chromatid exchanges, and micronucleus tests. Chromium carcinogenesis is described as an example. General conclusions and recommendations for the future are presented. (56 Refs)

36. THE CARCINOGENICITY OF CHROMIUM.

Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

A review is presented of interactions of trivalent and hexavalent chromium with biological materials, environmental and occupational chromium exposure, epidemiological and experimental studies of chromium carcinogenicity, and in vitro studies of chromium mutagenesis. Further studies are needed to determine whether trivalent chromium causes cancer and whether soluble and slightly soluble hexavalent salts differ in carcinogenic potency. The importance of smoking in chromium carcinogenesis needs to be established, as does the identification of the specific compound responsible for cancer in workers exposed to chromate. (98 Refs)

37. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

Nickel carcinogenesis research since 1975 is reviewed, with emphasis on new experimental techniques for studying carcinogenesis in vivo and in vitro. The subjects covered include epidemiologic studies, clinical investigations, carcinogenicity tests in animals exposed to nickel compounds by different administration routes, x-ray diffractometry and radiotracer studies of alpha-Ni3S2 metabolism, electron microscope studies of alpha-Ni3S2-induced tumors, cytogenetic and tumor transplantation studies, effects of nickel compounds on DNA synthesis, cell culture studies, bacterial mutagenicity tests, and effects of metals on viral and bacterial DNA polymerase. Prospects for future research on nickel carcinogenesis are summarized. (82 Refs)

38. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

In vitro bioassays for detecting the mutagenicity and potential carcinogenicity of metal compounds are reviewed. Assays discussed include the Salmonella typhimurium and Escherichia coli assays that quantitate the ability of metals to revert the bacteria to histidine prototrophy and to tryptophan prototrophy, respectively, and the use of Bacillus subtilis strains deficient in DNA repair to determine growth inhibitory effects of metals. Other bioassays examine the ability of metals to induce thioguanine or azaguanine resistance in Chinese hamster cells, enhance viral transformation in hamster cells, transform Syrian hamster cells, and induce chromosome aberrations in hamster and rat cells and human lymphocytes. Correlations between in vitro bioassays and in vivo carcinogenicity are discussed. (82 Refs)

39. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.

Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

A review is presented of mechanisms of mutagenesis, effects on DNA repair leading to comutagenesis, and possible reasons why carcinogenic metals are not mutagenic in microbial systems. A classification of mutagenesis mechanisms is based on the possible modes of action of metals: misreplication due to altered DNA or decreased fidelity of DNA polymerase, inhibition of proofreading, and mutagenesis via error-prone DNA repair. Excision repair, mismatch repair, and two other alternative pathways (not involving cleavage of the phosphodiester bond and subsequent repair replication characteristic of excision repair) are discussed with respect to effects on DNA repair leading to comutagenesis. Bacteria have an inducible, error-prone DNA repair system (SOS repair) whose activity results in mutagenesis. In one of the best studied examples of metal mutagenesis, chromate, little evidence exists for involvement of the SOS system. Arsenite exemplifies metals that may act as comutagens by inhibiting repair of damage to DNA caused by another agent. Comutagens would not be detected by standard screening methods. (48 Refs)

40. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.

Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

Present state of knowledge, public health implications, and required research are reviewed. Topics discussed include mechanism of DNA polymerization, fidelity of DNA synthesis, assays with polynucleotide templates, metal activators and nonactivating metal ions and fidelity, screening for metals that alter fidelity, fidelity of DNA synthesis with natural DNA templates, and mechanism of genetic miscoding by metals. A significant correlation exists between metals that decrease fidelity and those reported to be mutagenic and carcinogenic. To date greater than 40 metal compounds have been tested in graded concentrations for effects on fidelity of DNA synthesis. Compounds which increase infidelity by greater than 30% at two or more concentrations are scored positive: these included all the known mutagens/carcinogens (Ag, Be, Cd, Co, Cr, Mn, Ni, Pb), although evidence in the literature is equivocal for three metals. Of these, Cu++ increased misincorporation and Fe++ and Zn++ did not alter fidelity. With few exceptions these results have been confirmed. The general postulate that carcinogens can be identified by their interactions with DNA includes metals. (37 Refs)

41. USE OF LILIUM LONGIFLORUM, CV. ACE POLLEN GERMINATION AND TUBE ELONGATION AS A BIOASSAY FOR THE HEPATOCARCINOGENS, AFLATOXINS.

Dashek WV, Harman RL, Adlestein LB, Morton WA, Rapisarda BM, Chancey JC, Llewellyn GC
Dept. Biology, West Virginia Univ., Morgantown, WV, 26506
Environ Health Perspect; 40:267-278 1981

A previous study which showed that in Lilium longiflorum both pollen germination and tube elongation were enhanced by aflatoxin B1 (AFB1), suggested that a bioassay might be developed using these parameters. Reported are studies of effects of aflatoxins (AF) on seed germination and elongation of attached roots of certain crop plants (corn, peanut, barley), a comparison of the sensitivities of various plant and animal tissues to AF and a comparison of the sensitivities of the pollen bioassay and analytical methods for quantitating AF. While the pollen bioassay system is rapid, relatively simple and inexpensive, for quantitating AF, it is not as sensitive as current analytical methods and is also less sensitive than commonly employed animal bioassays. (43 Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
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2. THE CARCINOGENICITY OF ARSENIC.
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3. THE CARCINOGENICITY OF CHROMIUM.
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4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
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TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
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6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
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7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
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3. BENZENE AS A RISK FACTOR.
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Psychopharmacol Bull; 17(3):195-197 1981

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12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
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13. NUTRITIONAL MODULATION OF CANCER.
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15. EPIDEMIOLOGY.
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19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
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20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
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Acc Chem Res; 14(7):218-226 1981

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Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

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Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

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Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

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Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

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26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

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Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

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Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

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Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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IN VIVO MAMMALIAN SHORT-TERM TESTS

1. INITIATION/PROMOTION ASSAY FOR CHEMICAL CARCINOGENS IN RAT LIVER (MEETING ABSTRACT).

Pereira MA, Herren SL, Britt AL, Khoury M
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicologist; 1(1):155 1981

We have developed a short-term initiation/promotion assay in rat liver for the detection of chemical carcinogens. Male rats (175-200 gm) were po administered the chemical under test. One wk later tumor promotion by 500 ppm sodium phenobarbital in the drinking water was commenced. After 8 wk of promotion the rats were sacrificed and the liver stained and scored for gamma glutamyl transpeptidase (GGTase) positive foci. The appearance of GGTase positive foci was taken as an indication of the initiation of carcinogenesis by the chemical. In some cases partial hepatectomy was performed 24 hr prior to the administration of the test chemical in an attempt to increase the sensitivity of the assay. Acetylaminofluorene (AAF), aflatoxin B1 (AFB1) benzo(a)pyrene (BaP), diethylnitrosamine (DENA), 7,12-dimethylbenzo(a)anthracene (DMBA), dimethylnitrosamine (DMNA), N-methyl-N'-nitro-N-nitrosoguaninidine and urethane were positive in the assay while benzene (30 mmole/kg) was apparently negative. Phenobarbital promoted the response of AAF, AFB, DENA, DMBA and DMNA. Partial hepatectomy 24 hr prior to initiation increased the response of AAF, BaP, DENA and DMBA. The initiation/promotion assay in rat liver that includes 1) partial hepatectomy at 24 hr prior to administering the test chemical, 2) phenobarbital promotion and 3) GGTase foci as indication of carcinogenic activity; would appear to be sensitive to a wide variety of chemical carcinogens. (no Refs)

2. STUDIES ON MICRONUCLEI TIME RESPONSE AND ON THE EFFECTS OF MULTIPLE TREATMENTS OF MUTAGENS ON INDUCTION OF MICRONUCLEI.

Yamamoto KI, Kikuchi Y
Central Res. Div., Takeda Chemical Industries Ltd., Jusohonmachi 2-17-85, Yodogawa-ku, Osaka 532, Japan
Mutat Res; 90(2):163-173 1981

Specific effects revealed by the micronucleus assay were investigated. Micronuclei time responses for five mutagens were examined and micronucleus frequencies observed after single or multiple (5) treatments were compared for nine mutagens. Max frequencies of micronucleated RBC (MNEs) occurred at 24 hr post treatment for mitomycin C and triethylenemelamine, and 30 hr post treatment for busulfan, 6-mercaptopurine, and vincristine. Single and five-treatment schedules were equally effective in detecting alkylating agents and spindle poisons. The five-treatment schedule was more sensitive for detection of anti-metabolites. Most MNEs induced by a single treatment with alkylating agents and with anti-metabolites were type BS. After five treatments with these agents, MNEs classified as type RS were increased in a dose-dependent fashion. Types BL and RL were rarely observed with these agents; in the single- and five-treatment schedules using spindle poisons these types were seen with increasing frequency. (16 Refs)

3. EFFECTS OF PROLONGED CHEMICAL TREATMENT WITH CYCLOPHOSPHAMIDE AND 6-MERCAPTOPURINE IN THE DOMINANT LETHAL TEST SYSTEM.

Moreland FM, Sheu CW, Springer JA, Green S
Div. Toxicology, Food and Drug Admin., Washington, DC, 20204
Mutat Res; 90(2):193-199 1981

The effects of prolonged exposure (5 daily ip injections/wk for 10 wk) to cyclophosphamide (CP) and 6-mercaptopurine (6MP) were quantified using the dominant lethal assay. A dose-dependent reduction in fertility occurred in male rats treated with either compound. After final injection, male rats were housed with two virgin females/wk for 2 wk. The 10.0 mg/kg dose of CP caused a reduction in total implants per pregnant female and an increase in number of dead implants per female and of females with two or more dead implants. Negative results were obtained for all fertility criteria examined in 6MP-treated animals, except for a significant decrease in total number of implants per pregnant female at the 25 mg/kg level. Treatment with triethylene-melamine, the positive control compound, caused a significant decrease in number of total implants per pregnant female and a significant increase in the value for dead implants per total implants. (12 Refs)

4. ISSUES RELEVANT TO THE ASSESSMENT OF CHEMICALLY INDUCED CHROMOSOME DAMAGE IN VIVO AND THEIR RELATIONSHIP TO CHEMICAL MUTAGENESIS.

Anderson D, Richardson CR
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Mutat Res; 90(3):261-272 1981

Male Wistar rats were killed 6 or 24 hr after single or multiple exposure to clastogens, and bone marrow samples were prepared. Benzene, mitomycin C (MitC), ethyl methane sulfonate (EMS), trimethyl phosphate (TMP), and vinyl chloride (VC) constituted the groups of clastogens analyzed. A statistically significant increase in percentage of abnormal cells above negative control values, as well as some increases in individual categories of chromosome damage were observed after treatment with each clastogen. Dose-response relationships were evident for benzene, EMS, and MitC. For TMP and VC only one dose level was tested. Gap incidence increased above that of other types of chromosome damage. Multiple exposure at the same sampling time and with the same route of administration produced similar or smaller total amounts of chromosome damage than single exposure. Higher yields of damage were obtained at 6 hr than at 24 hr after treatment with benzene. Benzene also produced a similar level of damage after ip injection or a single 2 hr exposure by inhalation. (13 Refs)

5. APPLICATION TO BENZO(A)PYRENE FED RATS OF A PROPOSED SHORT-TERM IN VIVO CARCINOGEN SCREENING PROTOCOL (MEETING ABSTRACT).

Boyd JN, Misslbeck N, Campbell TC, Babish JG, Stoewsand GS
Department of Preventive Medicine, Cornell University, Ithaca, NY
Toxicologist; 1(1):36 1981

This study was undertaken to determine if induction of presumptive pre-cancerous lesions by benzo(a)pyrene (BP) could be predicted in a short-term treatment by demonstration of urinary mutagenesis and by increased concentration in the blood of the oncodevelopmental protein alpha fetoprotein (AFP). Existence of pre-cancerous lesions was confirmed by gamma glutamyl transpeptidase staining of liver sections from treated animals. Male weanling F344 Schf rats were fed semi-purified diets containing 0, 1, 100 or 1000 ppm BP with or without 0.05% sodium phenobarbital for six to thirteen wk. Blood was obtained at one to two wk intervals by cardiac puncture and plasma AFP levels were determined by sandwich type radioimmunoassay. Urine was collected for eight hr during the sixth wk of treatment. Glucuronidase-treated specimens were tested for mutagenesis in salmonella typhimurium strains TA98 and TA100 with and without microsomal activation. Liver specimens were stained for gamma glutamyl transpeptidase (GGT) activity and examined for presence of foci of altered cells. Those treatments resulting in elevated plasma AFP and mutagenic urine were associated with development of GGT-positive hepatic cell foci. This protocol could be applied early in the range finding phase of a carcinogenesis bio-assay to aid in selection of substances for long-term testing. (no Refs)

6. CHARACTERIZATION OF THE HEPATIC DNA DAMAGE CAUSED BY 1,2-DIBROMOETHANE USING THE ALKALINE ELUTION TECHNIQUE.

White RD, Sipes IG, Gandolfi AJ, Bowden GT
(c/o Sipes) Dept. Anesthesiology, Arizona Health Sciences Center, Univ. Arizona, Tucson, AZ, 85724
Carcinogenesis; 2(9):839-844 1981

Hepatic lesions induced by 1,2-dibromoethane (EDB: 25-75 mg/kg, ip) in male Swiss Webster mice were assessed by a modified alkaline elution assay. The major changes were use of 47-mm diameter filters and a microfluorometric technique to quantify the DNA. EDB administration caused a dose-dependent increase in DNA strand breaks. Allowing the DNA sample to remain on the filter in the presence of pH 12.3 buffer facilitated the conversion of alkali-labile sites to strand breaks detectable by the alkaline elution technique. To determine the presence of DNA cross-linking after EBD exposure, one-half of the hepatic nuclei were x-irradiated (200 rads) at 0 C. No EBD-induced DNA-DNA or DNA-protein cross-links were detected. This method may be useful for studying the nature of DNA damage induced by in vivo carcinogens. (22 Refs)

7. TISSUE AND SPECIES DIFFERENCES IN THE ABILITY OF THE PANCREATIC CARCINOGEN N-NITROSOBIS(2-OXYPROPYL)AMINE (BOP) TO INDUCE DNA DAMAGE (MEETING ABSTRACT).

Lawson T
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):32 1981

The production of DNA damage is a measure of a carcinogen's ability to induce potentially mutagenic and carcinogenic lesions in DNA. The ability of the carcinogen BOP to produce such lesions has been compared in target and non-target tissues of Syrian hamsters and MRC rats. In hamsters, BOP's carcinogenicity was dose-dependent, producing only pancreatic tumors at lower doses and also liver tumors at higher doses. In rats, BOP's carcinogenicity depended on the route of administration, and resulted in liver and colo-rectal tumors when given sc and prostate tumors when given po. Extensive DNA damage was produced in hamsters by 10 mg BOP/kg in the pancreas (target tissue) and the liver and salivary gland (non-target tissues). BOP persisted longer in the pancreas. At higher doses (20 and 40 mg/kg) persistance of damage was also seen in the liver. For the DNA damage in the pancreas there was an impressive dose response and a close correlation with the carcinogenicity of BOP. In rats, no DNA damage was seen in the pancreas (non-target tissue). The tissues in which BOP is a carcinogen all exhibited extensive and persistent DNA damage (liver, colon and prostate). These studies are being complemented by examinations of the in vivo metabolism of BOP and the nature and extent of alkylation produced. These results indicate that a potent carcinogen such as BOP is capable of producing potentially carcinogenic lesions in a variety of tissues, but that the subsequent carcinogenicity depends on one or more other factors, such as the capacity to produce a mitogenic response which will stimulate the tissue to cell division to 'lock in' the carcinogenic lesion. (no Refs)

IN VIVO NON-MAMMALIAN SHORT-TERM TESTS

8. RE-EVALUATION OF THE MUTAGENIC EFFECTS OF THE HAIR DYE P-PHENYLENEDIAMINE (BASE) IN THE SEX-LINKED RECESSIVE LETHAL TEST IN DROSOPHILA MELANOGASTER.

Blijleven WG
Dept. Radiation Genetics, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 90(2):137-141 1981

Results obtained with a purified sample of p-phenylenediamine in the Drosophila sex-linked recessive lethal test indicate that the compound is without mutagenic effect in this system. The only effect on treated males appears to be sterilization and toxicity. The findings contradict previous results, which could have reflected impurities not accounted for in the initial testing. (5 Refs)

BACTERIAL TEST SYSTEMS: SALMONELLA

9. MUTAGENIC ACTIVITY IN DIESEL EXHAUST PARTICULATES.

Nachtman JP, Xiao-bai X, Rappaport SM, Talcott RE, Wei ET
Standard Oil Co. California, Richmond, CA, 94802
Bull Environ Contam Toxicol; 27(4):463-466 1981

The mutagenicity of chloroform eluates of diesel exhaust particulate extracts was examined by Ames test with or without S-9 mix. Exhaust eluates produced S-9-independent mutagenic activity of approx 480 revertants/100 ug of extract/plate. The addition of live enzymes decreased mutagenic activity. After reduction of the exhaust extract with sodium borohydride, the S-9-independent activity was greatly diminished. Addition of S-9 to the reduced sample revealed the presence of S-9-dependent mutagenic activity. Results suggest the presence of nitroarene mutagens in diesel exhaust particulates. (12 Refs)

10. MUTAGENICITY IN SALMONELLA OF DYES USED BY DEFENCE PERSONNEL FOR THE DETECTION OF LIQUID CHEMICAL WARFARE AGENTS.

Nestmann ER, Kowbel DJ, Wheat JA
Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, K1A OL2, Canada
Carcinogenesis; 2(9):879-883 1981

Six indicator dyes capable of detecting chemical warfare agents in liquid form were tested for mutagenicity in the Salmonella typhimurium/rat microsome plate incorporation assay. Ethyl-bis(2,4-dinitrophenyl)acetate, Orasol Navy Blue 2RB (TD-4), and Eastman Fast Blue G-BLF induced dose-related increases in His+ reversion mutations in three or more of the S typhimurium tester strains (TA153, TA100, TA1537, TA1538, and TA98). Papers in which the dyes were impregnated were also mutagenic. Thiodiphenyl-4,4'-diazo-bis-salicylic acid was weakly mutagenic in the plate assay but strongly mutagenic in a fluctuation assay. Fluorescent Brilliant Yellow R and 2,5,2',5'-tetramethyltriphyenyl methane-4,4'-diazo-bis-beta-hydroxynaphthoic anilide were not mutagens. (16 Refs)

11. THE EFFECTS OF PRE-INCUBATION PERIOD AND NONHARMAN ON THE MUTAGENIC POTENCY OF 4-DIMETHYLAMINOAZOBENZENE AND 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE IN S. TYPHIMURIUM.

Lefevre PA, Ashby J
Central Toxicology Lab., ICI Ltd., Alderley Park, Macclesfield, Cheshire, England
Carcinogenesis; 2(9):927-931 1981

The mutagenic activities of liver carcinogens 4-dimethylaminoazobenzene (DAB) and 3'-methyl-4-dimethylaminoazobenzene (MeDAB) were tested using the Ames Salmonella typhimurium assay. Pre-incubation for 60 min produced a dose-dependent potentiation of DAB and MeDAB mutagenicity. The co-mutagen nonharman potentiated the mutagenic activity of DAB and MeDAB in direct plate assay (without pre-incubation). A 60-min preincubation in the presence of nonharman attenuated of mutagenic activity. (17 Refs)

12. DIFFERENTIAL PROTECTIVE EFFECTS OF ANTIOXIDANTS AGAINST CELL KILLING AND MUTAGENESIS OF SALMONELLA TYPHIMURIUM BY GAMMA RADIATION.

Ben-Hur E, Green M, Prager A, Rosenthal I, Riklis E
Nuclear Res. Centre-Negev, P.O. Box 9001, Beer-Sheva, Israel
J Radiat Res (Tokyo); 22(2):250-257 1981

Effects of gamma radiation from a 60Co source on cultures of Salmonella typhimurium were tested in the presence of antioxidants under oxic and anoxic conditions. The commercial mixture G-50 (6% propyl gallate [PG], 14% butylated hydroxytoluene, 8% butylated hydroxyanisole, 36% monoglyceride citrate, and 36% vegetable oil) protected against cell killing and induction of his+ mutations under oxic but not hypoxic conditions. When individual components of G-50 were tested, only PG exerted a protective effect. The amount of protection provided by the mixture was close to that afforded by hypoxia. The protection against cell killing was similar in magnitude to the protection against induction of mutation. No protective effect occurred in oxic cells when antioxidants were added to cells immediately after irradiation. (20 Refs)

13. STUDIES ON THE MUTAGENIC EFFECTS OF EXTRACTS DERIVED FROM AIRBORNE PARTICULATES WITHIN ONE YEAR IN DIFFERENTLY BURDENED AREAS USING THE AMES TEST.

Dehnen W, Tomingas R, Pitz R
Med. Institut fur Umwelthygiene, Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):351-366 1981

Season variations of the mutagenicity of extracts of suspended matter in air samples collected at monthly intervals in 1978 from three sites were assayed by the Ames test. The three sites were Duisburg (DU; mines), Dusseldorf (D; a residential city), and Krahm (K; rural district). Mutagenicity was tested in the presence of both S-9 and NADPH and with each cofactor alone. Results are presented as the number of revertants related to air vol, wt of suspended matter, wt of dried extract and to the amount of benzo(a)pyrene (BP) in the extract. Mutagenicity varied according to the BP concentration in the atmosphere with values highest in winter, lowest in summer. When mutagenicity was based on BP content, it was nearly constant throughout the yr at site DU or rose in summer (sites D and K). These results indicate that the larger part of the pollutants may originate from the same sources as BP (eg incomplete combustion). Direct mutagenicity (assayed without activating system) was somewhat higher in winter than in summer. However, these differences are minimal or lacking when mutagenicity was expressed as number of revertants per wt suspended matter or dried extract. Mutagenicity reached a max in summer, provided the number of revertants was related to BP concentration. The latter results indicate that the direct acting mutagens present in the air originated from other sources than that of BP (eg, automobile exhaust). Mean values of mutagenicity related to number of revertants per dry wt and wt of suspended matter did not differ among the three sites. It can be assumed that composition of particulate matter may be similar with respect to mutagens regardless of the level of pollution. (10 Refs) (In GER)

14. COMPARISON OF THE MUTAGENICITIES OF FOSSIL FUELS.

Pelroy RA, Sklarew DS, Downey SP
Dept. Biology, Pacific Northwest Lab., Richland, WA, 99352
Mutat Res; 90(3):233-245 1981

Mutagenicity of several shale oils as either unfractionated or partially purified mixtures was tested in the Ames assay system. Only the basic, basic tar, and neutral tar solvent fractions were mutagenic. Most of the mutagenic activity recovered from the Paraho and Livermore shales and the solvent refined coal process II heavy distillate were localized in basic and neutral tars (60-75% for the shale oils and greater than 90% for the coal distillate). More than 90% of mutagenic activity in the corresponding Sephadex LH-20 fractions was found in the methanol fractions. For the less active shale oils, Occidental and Geokinetics, the distribution of mutagens was approx equal between basic and tar fractions. Compared to the unfractionated crude synfuel materials, recoveries of mutagenic activity appeared greater for solvent fractions than for LH-20 fractions. Mutagenicity of the tested shale oils, estimated from genetic activity of both crudes and chemical fractions derived from the crudes, ranged over approx one order of magnitude. (15 Refs)

15. SOME CARCINOGENIC, MUTAGENIC, AND BIOCHEMICAL PROPERTIES OF PLATINUM ANTITUMOR COORDINATION COMPLEXES AND OF S-VINYL- AND S-ETHYLHOMOCYSTEINE.

Leopold WR
The University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):998-B 1981

It is known that cis-dichlorodiammineplatinum(II) (DDP), cis-dichlorobis(cyclopentylamine)platinum(II) (DCP), and the three stereoisomeric forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and of sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) each induced lung adenomas in A/JAX mice, while cis-DDP also initiated skin papillomas in CD-1 mice. Cis-DCP and cis-dichlorobis(pyrrolidine)platinum(II) induced sarcomas at the injection site in rats. Each of the above complexes was mutagenic for Salmonella typhimurium TA100, and the mutagenicity of the SHP and DDCP complexes was highly dependent on the stereoconfiguration of the 1,2-diaminocyclohexane ligand. No quantitative correlation of mutagenicity or tumorigenicity with electrophilic reactivity (as determined by reaction with DNA) or reported antitumor activity was found for the DDP, DDCP, and SHP complexes. The mutagenic and carcinogenic properties of S-vinylhomocysteine (vinthionine) were examined in relation to those of S-ethylhomocysteine (ethionine) to test a hypothesis that vinthionine might be a proximate carcinogenic form of ethionine. (no Refs)

16. TOXICITY, MUTAGENESIS AND CO-MUTAGENESIS OF CADMIUM (CD) IN SALMONELLA MUTANTS TA98 AND TA100 (MEETING ABSTRACT).

Rubin RJ, Kroll R
Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, MD, 21205
Toxicologist; 1(1):25 1981

The role of cadmium as a carcinogen has been controversial. In the widely used bacterial assay of Ames for mutagens/carcinogens the metals have routinely been reported to be negative. In the present study the mutagenesis and co-mutagenesis of Cd along with its toxicity was studied in TA98 and TA100. Cd, at the concentrations indicated, was added to the media used to prepare the solid agar plates onto which the test bacteria were poured. Exposure to Cd occurred during the 48 hr incubations on the solid agar. Toxicity tests were carried out on nutrient agar while mutagenesis and co-mutagenesis were performed on histidine-deficient agar. TA98 was inhibited 50% by 2.5 x 10(-6) M Cd but was uneffected by 2.5 x 10(-8) M and lower; TA100 was less sensitive and was inhibited 50% by 1.25 x 10(-4) M and was uneffected by 2.5 x 10(-5) M and lower. Zn, at non-toxic levels, completely protected against the toxicity of Cd at Zn: Cd M ratios of 4:1 for TA98 and 1:1 for TA100. At nontoxic levels Cd had no mutagenic effect on TA98 but increased the mutagenicity of a known direct-acting mutagen, hycanthone (Hyc) 3-4 fold. The same degree of enhancement of Hyc mutagenicity by non-toxic levels of Cd was seen in TA100. Lucanthone (Luc), an indirect-acting mutagen, has been shown to give rise to Hyc following S9 activation. No effect of Cd was seen on the mutagenicity of Luc in a S9 supplemented system, suggesting inhibition of activation, thereby offsetting Cd enhancement of any Hyc that would be formed. No effect of Cd was seen on another direct-acting mutagen, methylnitro-nitrosoguanidine. These data indicate that Cd may act as a co-mutagen for certain mutagenic agents and suggest a possible co-carcinogenic role for this metal. (no Refs)

17. THE INFLUENCE OF PROCARBAZINE (MIH) ON THE INDUCTION OF PROPHAGE LAMBDA IN ESCHERICHIA COLI K12 AND TOXIC EFFECTS ON SALMONELLA TYPHIMURIUM.

Lackner F, Schupbach ME
(c/o Schupbach) Biological Pharmaceutical Res. Dept., F. Hoffman-La Roche and Co. Ltd., CH-4002 Basel, Switzerland
Mutat Res; 90(3):247-254 1981

Procarbazine, a hydrazine derivative active against various malignancies, was found to lead to the formation of weakly mutagenic hydrogen peroxide at concentrations of 8-12 mg/plate in the Escherichia coli prophage lambda induction assay. No mutagenic effect was observed at equal concentrations in Ames test strains TA98 and TA100 of Salmonella typhimurium. (19 Refs)

BACTERIAL TEST SYSTEMS: NON-SALMONELLA

18. URINARY MUTAGENICITY ASSAY IN IDENTIFYING INDIVIDUALS WITH EXPOSURE TO GENOTOXICANTS IN THE RUBBER INDUSTRY (MEETING ABSTRACT).

Vainio H, Falck K, Sorsa M
Institute of Occupational Health, Helsinki, Finland
Symposium on Host Factors in Human Carcinogenesis, June 8-11, 1981, Cape Sunion, Greece International Agency for Research on Cancer; 1981

Several epidemiological studies confirm excess cancer mortality in the rubber industry. In trying to estimate the different levels of exposure, we have analyzed urinary mutagenic activity in the urine of workers in different jobs. The mutagenic activity was measured from concentrated urine samples using the sensitive bacterial fluctuation assay, both at the end of a normal working wk and after one mo vacation before returning back to work. Workers in certain job categories, especially those in the chemical mixing and weighing department as well as those in tire vulcanization, exhibited highly increased mutagenic activity in urine samples taken after a normal working wk. Bacteria strains sensitive to both base-pair substitution mutagens and frame-shift mutagens have been used. The mutagenicity due to smoking is detectable, especially with frame-shift strains and can thus be differentiated from mutagenicity caused by occupational exposure. The urinary mutagenicity assay appears to offer a possibility for identifying previously unsuspected chemical hazards yr before they become evident as the cause of irreversible pathologic changes in continuously exposed workers. By careful application of this test procedure, both the cause and the resultant incidence of cancer in individuals that work in high-risk environments may be reduced. (no Refs)

19. COMPARISON OF THE MUTAGENIC ACTIVITY OF DIALKYLNITROSAMINES IN ANIMAL-MEDIATED AND IN VITRO ASSAYS USING AN ESCHERICHIA COLI INDICATOR.

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Carcinogenesis; 2(9):909-914 1981

The mutagenicity of six dialkylnitrosamines was tested in intrasanguineous host-mediated and in vitro assays. In the host-mediated assay, Swiss albino mice were inoculated iv with Escherichia coli cells and immediately after with test compound. Within different time periods up to 300 min after exposure the mice were sacrificed and liver and spleen homogenates were plated on selective agar media. Yield of mutations in the host-mediated assay was in better agreement with carcinogenicity data than the mutation yield obtained in vitro using induced or uninduced rat liver S-9 fractions. (23 Refs)

20. QUANTITATION OF A MUTAGENIC METABOLITE PRODUCED FROM 1,2-DIMETHYLHYDRAZINE DURING LIPID INFLUENCED COLON CANCER DEVELOPMENT BY A BACILLUS SUBTILIS ASSAY.

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Diss Abstr Int [B]; 42(4):1330-B 1981

The positive correlation between intake of dietary fat and cancer of the colon is well documented. Studies were conducted using an experimental colon carcinogenesis model to determine the role of dietary fat in the metabolism of the colon carcinogen, 1,2-Dimethylhydrazine (DMH). Bacillus subtilis TKJ6321 was used to quantify fecal mutagen and postmitochondrial enzyme in the liver and the colon mucosa of rats fed diets variable in lipid content and treated ip with DMH. Corn oil or coconut oil were used as the source of lipid for the diets. During a 32 wk schedule rats were sacrificed and autopsied for evidence of adenocarcinoma of the colon. Fecal samples were extracted and assayed for mutagenic activity by B subtilis TKJ6321 as the microbial detector of mutagenicity. Rats fed corn oil in the diet and treated with DMH produced a significantly higher number of adenocarcinomas of the colon. When the lipid content of the diet was raised to 10% (wt/wt) corn oil markedly stimulated enzyme induction in animals receiving DMH treatment. This induction was especially pronounced in the mutagen-producing enzyme activity of the colonic mucosa. Treatment of rats with DMH induces enzyme in the liver and colon relevant for the conversion of this compound to a mutagenic species. The extent of enzyme activity is influenced by the type of lipid supplementing the diet as is subsequent colon tumor development. (no Refs)

FUNGAL CELL CULTURE TEST SYSTEMS

21. COMPARATIVE STUDY ON THE EFFECTS OF CYCLOPHOSPHAMIDE ON YEAST IN VITRO AND IN THE HOST-MEDIATED ASSAY: DNA DAMAGE AND BIOLOGICAL RESPONSE.

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Chem Biol Interact; 37(1):141-154 1981

Cyclophosphamide (CP), whether applied in its chemically activated form as 4-hydroperoxy-cyclophosphamide in vitro or in the host-mediated assay using rats, exhibits toxic and mutagenic effects on excision deficient yeast cells. The expression of these effects is examined during a prolonged postincubation in buffer and compared with the ability of activated CP to induce interstrand cross-links and DNA fragmentation. At comparable doses, we observe a close similarity of biological and biochemical effects in either test system. (Author abstract) (23 Refs)

22. TUMOUR PROMOTERS INDUCE MITOTIC ANEUPLOIDY IN YEAST.

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Nature; 294(5838):263-265 1981

A series of seven phorbol analogues and eight unrelated compounds were tested for induction of aneuploidy or crossing-over in assays using the D6 strain of Saccharomyces cerevisiae. A positive response was a three-fold or greater increase in frequency of aneuploid colonies in at least two separate experiments. All promoters tested were positive, while nonpromoters were negative. 12-O-Tetradecanoylphorbol-13-acetate (TPA) and phorbol-12-13-didecanoate (PDD) were positive while no significant increases in aneuploidly were observed with phorbol, phorbol monoesters, 4-O-methyl-TPA or 4alpha-PDD, which are also inactive as promoters on mouse skin. A dose-response curve for TPA showed dose-related increases in aneuploidy over the concentration range 0.02-5.0 ug/ml. Mezerein, a weak promoter but as potent as TPA in inducing many biochemical and morphological effects in cells, did not induce aneuploidy in the assay. The tumor promoters had no effect on the frequency of crossing-over. However, under identical conditions, the incomplete promoter mezerein induced mitotic cross-over at concentrations greater than 10 ug/ml whereas TPA was ineffective. Mezerein was the only compound which showed significant activity in increasing cross-over. The data presented do not indicate whether the assay of induced chromosome aneuploidly in yeast will be useful in detection of tumor promoting chemicals. (27 Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: MUTAGENICITY

23. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E
Merck Inst. for Therapeutic Res., West Point, PA, 19486
Mutat Res; 87(2):81-142 1981

The current literature on chemically induced specific locus mutations in the V79 Chinese hamster cell line are reviewed and evaluated. Characteristics of V79 cells, various genetic markers, and protocols for mutant induction by chemicals in the presence and absence of activation systems are described. The chemicals which were tested in V79 cells for mutagenic activity are listed. The usefulness of V79 cells for the screening of environmental chemicals which may be hazardous to humans is evaluated. Mutagenesis assays are discussed in relation to characteristics of the V79 cell line, genetic markers (hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus, reversion of HGPRT- mutants, ouabain-resistance, drug resistance, and auxotrophic, prototrophic and temperature-sensitive mutants) of V79 cells, and suggested and testing (toxicity and dose selection, standard mutagen treatment conditions, expression time, mutant selection, identification of phenotypic variants as presumptive genotypic variants, metabolic activation, cell-mediated mutagenesis, tissue homogenate-mediated mutagenesis, positive and negative controls, experimental design) protocols. Test performance is evaluated based on an analysis of the literature. The strengths and weaknesses of the V79 assay are considered. The role of the assay in mutagenicity and carcinogenicity testing programs is discussed. (162 Refs)

24. ASCORBATE IS NOT DETECTABLY MUTAGENIC IN THE L5178Y TK+/- CELL MUTATION ASSAY.

Amacher DE, Paillet SC
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Cancer Lett; 14(2):151-158 1981

Sodium ascorbate and ascorbic acid were tested at milliM concentrations for induction of gene mutations at the thymidine kinase locus in mouse lymphoma L5178Y TK+/- cells. Sodium ascorbate at concentrations greater than 0.5 milliM produced obvious cytotoxicity but no dose-related mutagenicity. Inclusion of catalase during the 3 hr exposure period abolished the cytotoxic effects of sodium ascorbate. Increased pH was not responsible for ascorbic acid cytotoxicity. Toxic moieties were formed from freshly dissolved ascorbate in the absence of cells. It is suggested that ascorbic acid is not mutagenic in mammalian cells under normal physiological conditions. (18 Refs)

25. QUANTITATIVE MUTAGENESIS AND MUTAGEN SCREENING WITH MAMMALIAN CELLS: TOWARD A COMPREHENSIVE CHINESE HAMSTER GENETIC TOXICITY SYSTEM (MEETING ABSTRACT).

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Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Toxicologist; 1(1):40 1981

We have employed Chinese hamster ovary (CHO) cells to develop and define a mutational assay at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. Coupled with S9 metabolic activation system, the CHO/HGPRT assay permits quantification of gene mutation and cytotoxicity induced by various classes of mutagens including 3 aklanesulfonates, 2 alkylsulfates, 3 nitrosoguanidines, 3 nitrosoureas, 19 heterocyclic mustards (ICR compounds), 6 platinum(II)chloroammines, 7 quinolines, 8 nitrosamines, 3 haloethanes, 4 polyaromatic hydrocarbons. Such study elucidates the structure-activity relationship for a given class of direct-acting mutagens. All carcinogens investigated, except ICR 191, showed mutagenic activity; and all noncarcinogens were nonmutagenic. The CHO/HGPRT system can also simultaneously measure mutagen-induced chromosome aberration and sister chromatid exchange (SCE) which led to the development of the Multiplex CHO Genetic Toxicity Assay. Recent studies have shown that it is feasible to determine chromosomal deletion and loss using a CHO/human hybrid cell line and to develop a Chinese hamster system for studies of induction of mutation at the HGPRT locus, chromosome aberration and SCE of peripheral blood lymphocytes. The use of such a comprehensive Chinese Hamster Genetic Toxicity System consisting of these four assays at the cellular and organismic level should enable a sensitive and reliable identification of suspected environmental mutagens. (no Refs)

26. MUTAGENICITY AND CYTOTOXICITY OF HALOETHANES AS STUDIED IN THE CHO/HGPRT SYSTEM.

Tan EL, Hsie AW
Graduate Sch. Biomedical Sciences, Univ. Tennesee, Oak Ridge, TN
Mutat Res; 90(2):183-191 1981

Mutagenic and cytotoxic effects of ethylene dibromide (EDB), ethylene bromochloride (EBC), and ethylene dichloride (EDC) as quantified in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase mammalian cell gene mutation assay are reported. All haloethanes tested exhibited mutagenic activity in the presence or absence of S9, in the order EDB greater than EBC greater than EDC. When tested as direct-acting agents, EDM, EBC, and EDC reduced cell survival to 50% at approx 3, 6, and 50 mM, respectively. Cell survival decreased with further increases in haloethane concentration. Cell survival dropped exponentially over a treatment time of 24 hr, but the mutagenic activity attained a max at approx 5 hr. The haloethanes were 5-25x more toxic in the presence of S9 than in its absence. S9-induced toxic metabolites were also more mutagenic to the cells. Such increased toxicity is NADPH-dependent. (22 Refs)

27. TOXICITY AND MUTAGENICITY OF HYDRAZINE AND THREE METHYLATED DERIVATIVES IN L5178Y MOUSE LYMPHOMA CELLS (MEETING ABSTRACT).

Rogers AM, Back KC
Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH
Toxicologist; 1(1):40 1981

Heritable effects can be detected in mammalian cells in culture using changes in gene functions as an end-point. The function of different genes can be revealed by the use of selective agents. The four selective systems used here are ouabain, thymidine, thioguanine and cytosine arabinoside. Previous work with a series of compounds in L5178Y mouse lymphoma cells has indicated that they may possess mutagen specific activity. Hydrazine, monomethylhydrazine (MMH), 1,1-dimethylhydrazine (UDMH) and 1,2-dimethylhydrazine (SDMH) have been examined for toxicity and mutagenic potential. The compounds exhibit marked differences in toxicity. MMH is the most toxic compound followed by hydrazine, UDMH and SDMH. This correlates well with the toxicity of these compounds in vivo as the same relative toxicities were observed in the mouse. Hydrazine, UDMH and SDMH induced mutation in the thymidine selective system in the absence of extraneous metabolic activation. Dose-response curves were produced for these compounds. MMH did not induce thymidine mutation in the presence or absence of extraneous metabolic activation. All four compounds were negative in the ouabain, thioguanine and cytosine arabinoside selective system. Induction of mutation by hydrazine and UDMH is correlated with toxicity. This is not the case for SDMH-induced mutation. Hydrazine, UDMH and SDMH appear to have different modes of action in the cell. (no Refs)

28. POTENCY OF AFLATOXIN B1 AND AFLATOXIN M1 IN CYTOTOXICITY AND DNA REPAIR ASSAYS (MEETING ABSTRACT).

Green CE, Rice DW, Hsieh DP, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):42 1981

Although the acute toxicity and carcinogenicity of aflatoxin B1 (AFB1) has been thoroughly documented, relatively little is known of the potency of aflatoxin M1 (AFM1), a hydroxylated metabolite of AFB1. Therefore, the cytotoxicity and genotoxicity of AFB1 and AFM1 were compared using in vitro system of primary cultures of rat hepatocytes. Hepatocytes were cultured for 20 hr (2.5 x 10(6) cells/dish) in hormone supplemented culture medium. The incubation was continued for an additional 24 hr with the test chemicals and 0.5 uCi/ml [3H] thymidine ([3H]TdR). Cytotoxicity was assessed by measuring lactate dehydrogenase released into the culture medium. Both AFB1 and AFM1 were potent cytotoxins. LDH levels w ere elevated significantly above controls for AFB1 at 0.1 ug/dish and for AFM1 at 0.6 ug/dish. However, LDH concentrations rose to the same max of approx 200% of controls for AFB1 and AFM1 at a dose of 1.2 ug/dish. Genotoxicity was assessed by measuring unscheduled DNA synthesis by two different methods, incorporation of [3H] TdR into trypsin-resistant acid-precipitable material and autoradiographic analysis. AFB1 and AFM1 were both positive and about equally potent in the DNA repair assay using either technique. In vivo experients indicate a higher level of DNA binding for AFb1 than AFM1. There are two plausible explanations for the DNA repair data; 1) AFB1 and AFM1 bind to DNA to approx the same extent in the hepatocyte culture system, 2) less AFM1 is covalently bound to DNA than AFB1 but AFM1 adducts are more efficiently repaired. (1 Ref)

MAMMALIAN CELL CULTURE TEST SYSTEMS: CYTOGENETIC TESTS

29. GENOTOXIC AND CYTOCIDAL EFFECTS OF THREE ELECTRON AFFINIC SENSITIZERS ON HYPOXIC AND AERATED MAMMALIAN CELLS (MEETING ABSTRACT).

Geard CR, Spunberg JJ, Rutledge-Freeman M, Harding TA
Radiological Research Laboratory, Department of Radiology, Cancer Center, Institute of Cancer Research, Columbia University, College of Physicians and Surgeons New York, NY, 10032
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

The cytocidal effect of misonidazole on hypoxic mammalian cells is mediated at low cell survival (10%) via an induced interphase cell death. When about 50% of cells survive sensitizer treatment, cell death is about equally due to induced chromosomal aberrations (post-mitotic death) and interphase death, for misonidazole, desmethylmisonidazole and SR 2508. Further, there is a cell cycle stage specific effect which is seen as a progressive chromosomal degeneration of putative late G1-early S phase cells. Cells from these stages also show substantially enhanced frequencies of sister chromatid exchanges (SCE's), to levels similar to those found with potent mutagen-carcinogens. A 72 hr treatment of aerated cells with misonidazole and desmethylmisonidazole results in about the same level of cell kill as that attained by a 4 hr treatment of hypoxic cells with all three sensitizers. By contrast the Stanford Research compound SR 2508 is three x more cytotoxic to aerated cells after a 72 hr drug exposure. In the aerated cells SCE's are maximally enhanced about two fold, but chromosomal aberrations do not follow levels of cell kill. Hence sensitizer treated aerated cells largely die in interphase. These data indicate that all three agents are potentially genotoxic to naturally hypoxic cells while the greater cytocidal effect of SR 2508 in aerated cells warrants close observation. (no Refs)

MAMMALIAN CELL CULTURE TEST SYSTEMS: TRANSFORMATION

30. NEOPLASTIC TRANSFORMATION ASSAY WITH BALB/C 3T3 CELLS. ANALYSIS OF RESULTS WITH 70 CODED SAMPLES (MEETING ABSTRACT).

Sivak A, Lobb AM, Tu AS
Arthur D. Little, Inc., Cambridge, MA, 02140
Toxicologist; 1(1):131 1981

Exposure of certain populations of mouse BALB/c 3T3 cells to chemical carcinogens results in morphological transformation in the cell culture that can be identified and quantified. In the assay validation, 15 uncoded and 70 coded chemicals comprising a series of known carcinogens and noncarcinogens were tested using a standard protocol. Among the chemical classes tested, polycyclic aromatic hydrocarbons, direct-acting alkylating agents, activated aromatic amine metabolites and certain metal carcinogens gave positive responses. Aromatic amines, nitrosamines and other chemicals, such as natulan and cyclophosphamide, that require metabolic activation to exhibit activity, did not induce neoplastic transformation, although aniline was positive. The hormones ethynylestradiol, progesterone and diethylstilbesterol, which are likely epigenetic carcinogens, were not active in this system. Statistical analyses of the data reveal that: (1) the range of spontaneous transformation frequency has a mean value of 0.28 foci/plate; (2) the induced transformation frequency of the positive control (3-methylcholanthrene, 2 ug/ml) has a mean value of 2.6 foci/plate; (3) at control values above the cumulative mean, a doubling of transformation frequency in treated cultures is a statistically significant positive effect (alpha less than or equal to 0.05). At the control values below the cumulative mean, statistical significance is achieved only at higher treated to control response ratios, which rise sharply as control values approach zero. (4) The relationship of the untreated control response to the positive response is not a simple background incidence. (no Refs)

31. IN VITRO TRANSFORMATION BY HYPOXIC CELL SENSITIZERS (MEETING ABSTRACT).

Hall EJ, Miller RC
Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY, 10032
Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committee for Radiation Oncology Studies; 1981

One of the compounds developed to replace misonidazole is desmethylmisonidazone which has a shorter half-life in vivo than Misonidazone, and SR 2508 which is more hydrophilic and does not cross the blood brain barrier as readily. The compounds have been tested for their oncogenic potential using C3H 10T1/2 cell in vitro. These mouse embryo fibroblast derived cells normally exhibit contact inhibition and stop growing when they have produced a confluent sheet of cells. When exposed to x-rays, neutrons or chemical agents, transformed foci are produced consisting of densely stained piled up cells, with criss-crossing and swirling of cells at the edge of the clone. For Misonidazole, the incidence of transformed foci per surviving cell was determined for a range of concentrations from 0.1 to 10 mM, using a 3-day exposure time. At 1 mM, which approximates to the max concentration attainable in the serum of patients on treatment with Misonidazole, the transformation incidence is comparable to that produced by 1 gray of x-rays. Desmethylmisonidazole produced transformation at a similar rate to Misonidazole, but SR 2508 produces a five-fold higher incidence of transformed foci for a given drug concentration and exposure time. (no Refs)

32. PROMOTION OF IN VITRO MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS (MEETING ABSTRACT).

Rivedal E, Sanner T
Laboratory for Environmental and Occupational Cancer, Radiumhospitalet, Oslo, Norway
Symposium on Host Factors in Human Carcinogenesis, June 8-11, 1981, Cape Sunion; Greece International Agency for Research on Cancer; 1981

Sequential exposure in the hamster embryo cell transformation bioassay has been used to study the effect of different tumor promoters and non-promoting analogues. One day after seeding of the target cells, the test chemicals are added. After 7 days of incubation, the dishes are fixed, stained and inspected for transformation. In studies of the effect of promotors, the test chemical was removed after 3 days, the dishes washed and the promoter added in new medium. In experiments where the cells were exposed sequentially to benzo(a)pyrene (BP) and the tumor promoter tetradecanoylphorbol acetate (TPA), a tenfold enhancement of the transformation frequency was observed compared to when the compounds were tested separately. When TPA was given prior to BP, no enhancement was observed. Phorbol didecanoate (PDD) showed an almost similar strong effect to that of TPA, while the two analogues 4alphaPDD and 4-O-Me-TPA were negative. In other experiments we have found that cigarette smoke extract and some metal ions (Ni++ and Cd++) also show promotion-like effects on morphological transformation of hamster embryo cells. Thus, this system may be of value in studies of tumor promoters. (no Refs)

33. INITIATION OF C3H/10T1/2 TRANSFORMATION BY DIRECT-ACTING ALKYLATING AGENTS (MEETING ABSTRACT).

Boreiko CJ, Frazelle JH, Abernethy DJ, Ragan DL
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
In Vitro; 17(3):201 1981

C3H10T1/2 Cl 8 mouse embryo fibroblasts can be oncogenically transformed by numerous carcinogens, but are reported to be relatively insensitive to the oncogenic potential of simple alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). This lack of sensitivity is surprising in view of reports that MNNG is mutagenic for these cells. Since C3H/10T1/2 transformation can be demonstrated to progress through the discrete stages of initiation and promotion, we have examined the ability of alkylating agents to act as initiating agents. MNNG (0.1-0.5 ug/ml) and formaldehyde (0.1-2.5 ug/ml) produced transformed foci in a dose dependent fashion if carcinogen treatment with 0.1 ug/ml of the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA). Foci were produced in 19 of 65 dishes treated with 1 ug/ml formaldehyde + TPA, and in 24 of 62 dishes treated with 0.5 ug/ml MNNG + TPA. Foci were rarely observed in solvent treated controls or MNNG treated dishes not treated with TPA. Phorbol did not promote focus production by MNNG. In contrast, TPA inhibited focus production by 1 ug/ml concentrations of the transforming agent 3-methylcholanthrene. These findings suggest that, when used for the detection of carcinogens, the C3H/10T1/2 transformation bioassay should be conducted in the presence and absence of appropriate tumor promoters. (no Refs)

34. NEOPLASTIC TRANSFORMATION OF HUMAN EPITHELIAL CELLS IN VITRO AFTER EXPOSURE TO CHEMICAL CARCINOGENS.

Milo GE, Noyes I, Donahoe J, Weisbrode S
Comprehensive Cancer Center, Ohio State Univ., 410 West 12th Ave., Columbus, OH, 43210
Cancer Res; 41(12):5096-5102 1981

Human foreskin epithelial cells were transformed to an anchorage-independent state of growth (in soft agar) and neoplasia (invasion of chick embryonic skin in vitro). Aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, propanesultone, beta-propiolactone, or UV absorbance at 254 nm were used successfully as carcinogens. These foreskin epithelial cells, like human foreskin fibroblasts, were readily transformed when treated in S phase but, unlike the transformed fibroblasts, expression of cellular neoplasia did not require an extended period of time in culture. The invasive features of the transformed human epithelial cells in chick embryonic skin in vitro simulated squamous cell carcinoma. (Author abstract) (29 Refs)

35. EFFECTS OF DEXAMETHASONE AND CORTISONE WITH X-RAY IRRADIATION ON TRANSFORMATION OF C3H 10T1/2 CELLS.

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Nature; 293(5836):97-98 1981

It is reported that dexamethasone (DEX) and cortisone (CORT) do not suppress radiation transformation of C3H 10T1/2 cells in vitro. DEX (10-7M) or CORT (10-7M) was added to the cultures immediately after irradiation (400 rad of x-rays) and subsequently added at each medium change for the 6-8-wk transformation assay. Dense cell foci were identified and scored as follows: Type 1 were abnormally dense but normal in other respects; Type 2 were large, moderately stellate, and tumorigenic in 60-75% of inoculated mice; and Type 3 were large, highly stellate, and tumorigenic in 80-100% of inoculated mice. The fraction of dishes used that contained Type 3 transformants was 0/40 for controls (no treatment), 12/77 for irradiation alone, 11/78 for CORT alone, 1/78 for DEX alone, 41/76 for irradiation and CORT, and 23/75 for irradiation and DEX. The fractions for cell Types 2 and 3 were 0.40, 26/77, 16/78, 3/78, 54/76, and 34/75, respectively. The results show that for cells exposed to both CORT and x-rays there seemed to be a synergistic response for the induction of malignant transformation. For DEX and x-rays, there was a higher yield of transformants than expected for an additive effect, but it was not significantly greater than the yield of transformants observed for radiation alone or for the expected additive effect of the combined treatments. It is speculated that when clinical efficacy is similar that DEX may give a decreased risk of tumor formation compared with CORT. (19 Refs)

36. ASSESSMENT OF ENVIRONMENTAL CONTAMINATION ASSOCIATED WITH A MAMMALIAN CELL TRANSFORMATION ASSAY.

Sansone EB, Losikoff AM, Lebherz WB, Poiley JA

Environmental Control and Res. Lab., Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701

In Vitro; 17(9):811-815 1981

To estimate worker exposures to, and environmental contamination from, test chemicals and organic solvents used in an in vitro assay to assess the carcinogenic potential of chemicals, sodium fluorescein, a noncarcinogenic fluorescent material, was dissolved in tissue culture medium used to maintain early passage hamster embryo cells. Personal and environmental samples were taken over a 14-day period. The assay was performed according to standard procedures in a ventilated glove box or laminar flow safety cabinet. Considerably more than 99% of the chemical contamination found was recovered from the interiors of the glove box and hood and from disposable equipment. Contamination outside the containment units (less than 1 ug) resulted from intralaboratory transport of chemicals, treated cultures, and contaminated equipment. We conclude that the standard operating practices and procedures provided adequate safeguards for personnel and the environment. (Author abstract) (8 Refs)

37. SENSITIZERS, PROTECTORS AND ONCOGENIC TRANSFORMATION IN VITRO (MEETING ABSTRACT).

Miller RC, Osmak R, Zimmerman M, Hall E

Radiological Research Laboratory, Columbia University College of Physicians and Surgeons, New York, NY, 10032

Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

Systems developed to assay oncogenic transformation in vitro represent a rapid and powerful tool to screen and compare new radiosensitizers for their carcinogenic potential. An establishe d line of mouse embryo fibroblasts (C3H/10T1/2 cells) has been used to determine the incidence of transformation produced by a variety of 2 and 4 substituted nitroimidazoles; these include metronidazole, desmethylmisonidazole, misonidazole, SR 2508, SR 2555, RO-07-0741, RSU-1047 and RSU-1021. Most of these sensitizers produce a similar level of transformation; for example a three day exposure of aerated cells to a concentration of 1 mM of the drug results in a transformation incidence comparable to 1 Gy of x-rays. The notable exception is SR 2508 which produces a five-fold higher incidence of transformation. The potential carcinogenicity of sensitizers must be considered in choosing which of the currently available new drugs is to be used in clinical trials as a alternative to misonidazole. Superoxide dismutase (SOD), a known free radical scavenger, has been shown to reduce the level of transformation produced by radiation and sensitizers if present during the exposure and during the six wk incubation period required for the expression of transformed foci. (no Refs)

38. HORMONE AND NUTRITIONAL FACTORS AS REGULATORS OF X-RAY INDUCED TRANSFORMATION (MEETING ABSTRACT).

Borek C

Radiological Research Laboratory and the Department of Pathology, Columbia, OH

Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committee for Radiation Oncology Studies; 1981

Epidemiology and experimental animal data indicated that hormones and dietary factors play a role in modifying the incidence of cancer. Cell cultures offer defined systems for evaluating at a cellular level the direct involvement of these factors on the oncogenic potential of radiation, chemical carcinogens and chemotherapeutic agents. Using short term cultures of diploid hamster embryo cells and the heteroploid mouse cell line C3H 10T1/2 we have investigated a) the effects of retinoids, selenium, and dietary products derived from protein pyrolysates on radiation induced transformation, and b) the induction and/or expression of radiation and chemically induced in vitro transformation under hypothyroid conditions and hyperthyroid conditions. Our data indicate selenium and retinoids inhibit radiation induced transformation as well as the promotional effect by the tumor promotor tetradecanoylphorbol acetate and that protein pyrolysates act synergistically with radiation and potentiate radiation oncogenesis. We also find that the removal of thyroid hormone inhibits radiation and chemically induced transformation and that the addition of T3 at levels of 10(-11) to 10(-7) results in cell transformation which is dose dependent. (no Refs)

COMPARATIVE RESULTS FROM MULTIPLE TEST SYSTEMS

39. A COMPARATIVE GENOTOXICITY STUDY OF CHLOROGENIC ACID (3-O-CAFFEOYLQUINIC ACID).

Stich HF, Rosin MP, Wu CH, Powrie WD
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 West 10th Avenue, Vancouver, British Columbia V6T 1W5
Mutat Res; 90(3):201-212 1981

Genotoxicity of chlorogenic acid was evaluated in three different bioassays that depend on different tester cells and endpoints: reverse mutation in Salmonella typhimurium, gene conversion in Saccharomyces cerevisiae, and chromosome aberration in Chinese hamster ovary cells (CHO). No significant increase in mutagenesis in either Salmonella tester strain TA98 or TA100 was observed with or without addition of S9 mixture. A significant increase in his+ reversion frequency occurred when the strains were exposed to a mixture containing both Mn++ and chlorogenic acid. Addition of Cu++ was without effect. Neither transition metal induced his+ revertants alone. Caffeic acid produced a similar response pattern, but quinic acid was not mutagenic even in the presence of Mn++. Chlorogenic acid induced a greater than 2x increase in tryptophan (trp+) conversion frequency at non-toxic concentrations. Presence of S9 suppressed the response and transition metals enhanced it. Chlorogenic acid was also found to be a direct acting clastogen. In the presence of Mn++, chromatid breaks and exchanges were induced by chlorogenic acid at doses 10x lower than required by chlorogenic acid alone. (31 Refs)

40. MUTAGENIC AND CYTOTOXIC EVALUATION OF PLUTONIUM-244 (MEETING ABSTRACT).

Andrews TK, Samuel JE, Frazier ME
Biology Department, Pacific Northwest Laboratory, Richland, WA, 99352
In Vitro; 17(3):222 1981

The low specific activity of 244Pu enabled us to conduct a study using in vitro assays to determine the chemical mutagenicity and cytotoxicity of this metal. The effects of this isotope were compared to those of 238Pu and 239Pu to distinguish chemical effects from those caused by radiation. Mutagenicity was determined by the CHO-K1 (Chinese Hamster Ovary) assay, which measures forward mutation of the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. No significant increase in mutation frequency was observed at media concentrations up to 5 ug/ml; however, this isotope was mutagenic at concentrations above 6 ug/ml. A clonal growth assay (VERO), developed at this laboratory, was employed to determine cytotoxicity. As a measure of toxicity, this assay uses the 50% relative plating efficiency concept (RPE 50) ie, concentration of test material that produces a plating efficiency which is 50% of the control value. Concentration-response curves with the VERO growth assay show that 244Pu has an RPE 50 of 0.12 ug/ml, ranking it with the more toxic metals, ie, V greater than Cr greater than Ru greater than 244Pu greater than Cd greater than Hg. (no Refs)

41. MUTAGENICITY OF COSMETICS INGREDIENTS LICENSED BY THE EUROPEAN COMMUNITIES.

Gocke E, King MT, Eckhardt K, Wild D
Zentrallabor fur Mutagenitatsprufung, Deutsche Forschungsgemeinschaft, Breisacher Str. 33, D-7800 Freiburg/Breisgau, W. Germany
Mutat Res; 90(2):91-109 1981

Cosmetic ingredients allowed by the guidelines of the Council of the European Communities (27 July 1976) were investigated for mutagenicity in the Salmonella/microsome assay (SAL-m), the Basc test on Drosophila (Basc), and the micronucleus test on mouse bone marrow (MN). Of the 31 chemicals tested, 15 were mutagenic in SAL-m. Five of these were also mutagenic in Basc and two in the MN test. Only one compound, pyrogallol, was active in all three test systems. None of the compounds positive in the two eukaryotic systems was inactive in the SAL-m assay, which underlines the sensitivity of the Ames test with regard to various mutagens. Of the compounds positive in the SAL-m test, seven would not have been recorded if only the generally used Vogel-Bonner medium had been used. Of these substances, two were mutagenic in one or the other of the two eukaryotic test systems. (62 Refs)

42. MUTAGENICITY OF A SERIES OF HEXACOORDINATE CHROMIUM(III) COMPOUNDS.

Warren G, Schultz P, Bencroft D, Bennett K, Abbott EH, Rogers S
Dept. Chemistry, Montana State Univ., Bozeman, MT, 59717
Mutat Res; 90(2):111-118 1981

A series of 17 substitutionally inert chromium(III) compounds were synthesized and their genetic toxicity investigated in a differential DNA repair assay (DR) or the Salmonella histidine reversion assay (Ames assay). Genetic toxicity in both systems was critically dependent upon the ligand composition of the chromium(III) complexes. Compounds tested showed a parallel between mutagenicity in the Ames test in Salmonella and differential inhibition in the DR test in Escherichia coli. The greater the differential inhibition in the repair test, the more likely it was that a compound would be mutagenic in the Salmonella system. Four of the 17 compounds tested were positive in both systems, while 4 compounds were less active in the repair assay and negative in the Ames test. The remaining nine were negative in both assays. Three of the four most active complexes had four stable aromatic amine ligands, a charge of plus one, and two more labile ligands in a cis-configuration. Chromium(III) in the proper ligand environment can have considerable genetic toxicity and could represent one of the several possible ultimate species in a mechanism for chromium mutagenesis and carcinogenesis. (36 Refs)

43. MUTAGENICITY SCREENING OF ANESTHETICS FOR FISHES.

Yoshimura H, Nakamura M, Koeda T
Second Assay Div., Natl. Veterinary Assay Lab., 1-15-1 Tokura, Kokubunji-shi, Tokyo 185, Japan
Mutat Res; 90(2):119-124 1981

Anesthetics used in the handling of commercially valuable fish were studied for genetic toxicity. Eugenol, phenthiazamine, and tricaine were tested for mutagenicity in the rec assay with Bacillus subtilis strains M45 (rec-) and H17 (rec+), and in the reverse mutation assay with Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, and TA1538. No DNA damage was detectable for any of the compounds in the repair assay. In the mutagenicity studies, phenthiazamine gradually increased the revertant colonies in strains TA100, TA98 and TA1537 in the presence of S9 mix in a dose-dependent fashion. Neither eugenol or tricaine were mutagenic in any strain in the presence or absence of S9 mix. (14 Refs)

44. MUTAGENICITY OF ALKYL GLYCIDYL ETHERS IN THREE SHORT-TERM ASSAYS.

Thompson ED, Coppinger WJ, Piper CE, McCarroll N, Oberly TJ, Robinson D

Miami Valley Lab., Procter and Gamble Co., P.O. Box 39175, Cincinnati, OH, 45247

Mutat Res; 90(3):213-231 1981

Effect of alkyl chain length on the mutagenic potential of glycidyl ethers was examined in three in vitro assays, the Salmonella/mammalian microsome assay, the L5178Y mouse lymphoma assay, and by unscheduled DNA synthesis induced in WI38 human diploid fibroblasts. Glycidol, ethyl glycidyl ether, butyl glycidyl ether, and hexyl glycidyl ether were positive in the Salmonella revertant assay with or without metabolic activation, although enhancement of the response was seen in the presence of S9. Octyl glycidyl ether, decyl glycidyl ether, and dodecyl glycidyl ether induced a weak mutagenic response only in the presence of S9. Tetradecyl glycidyl ether was negative in this assay. In the mouse lymphoma assay, glycidol and the ethyl, butyl, and hexyl glycidyl ethers gave positive responses with or without S9. Octyl, dodecyl, and tetradecyl glycidyl ethers were negative. In the unscheduled DNA synthesis assay, positive responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for butyl glycidyl ether with S9 and ethyl glycidyl without S9, but other compounds were negative in this assay. (18 Refs)

45. CARCINOGENICITIES OF QUINOLINE DERIVATIVES IN F344 RATS.

Fukushima S, Ishihara Y, Nishio O, Ogiso T, Shirai T, Ito N

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Cancer Lett; 14(2):115-123 1981

Carcinogenicity of the quinoline derivatives 6-nitroquinoline (6NQ), 8-nitroquinoline (8NQ), 6-methylquinoline (6-MQ), 8-methylquinoline (8MQ), 8-hydroxyquinoline (8HQ), and 5,7-dibromoquinoline (5,7DQ) was assayed in F344 rats. Animals were fed diets containing 0.05% 6NQ, 0.1% 8NQ, 0.05% 6MQ, 0.05%8MQ, 0.1%8HQ, or 0.1% 5,7DQ ad libitum for 104 wk or until moribund. 8NQ induced forestomach tumors in both male and female rats, including squamous cell papillomas in 28/30 males and 36/37 females, and squamous cell carcinomas in 20/30 males and 24/37 females. The other derivatives tested were not carcinogenic in F344 rats. 6NQ induced areas of focal hyperplasia in forestomach tissue. The results indicate a discrepancy between mutagenic potential of these compounds as measured in the Ames Salmonella/microsome assay and their carcinogenicity in vivo. (13 Refs)

EVALUATIONS, REVIEWS AND OTHER RELATED STUDIES

46. SECOND ANNUAL REPORT ON NATIONAL CANCER INSTITUTE AND ENVIRONMENTAL PROTECTION AGENCY PROJECTS.

Department of Health and Human Services
Public Health Service, NIH, Bethesda, MD
Second Annual Report on National Cancer Institute and Environmental Protection Agency Projects. Bethesda, MD, National Cancer Institute, 384 pp., 1981.

Current projects underway under the auspices of the National Cancer Institute and the Environmental Protection Agency are described. Progress reports are presented for the following: a data base for chemicals identified in human biological media; in vivo analysis of UV-B-induced photooxidations; use of the hairless mice for carcinogenesis studies; chronic toxicity and carcinogenicity to rats and mice of chloroform in drinking water; the effects of carcinogens, mutagens, and teratogens on non-human (aquatic) species; the cost effectiveness of two types of personal UV-B dosimeters; the effects of varying doses of UV on mammalian skin; immunodiagnostic markers for breast cancer; antigens on human lymphoid organs for the immunodiagnosis of leukemias and lymphomas; human epithelial cell metabolic activation systems for use with human cell mutagenesis; evaluation of the transformation assay using C3H 10T1/2 cells for use in screening chemicals for carcinogenic potential; national mortality data bases for environmental epidemiology; epidemiologic field studies on ecological relationships between specified toxic substances and cancer morbidity and mortality; an epidemiologic study of populations in Turkey previously exposed to hexachlorobenzene; a case control study of lung, pancreas, and stomach cancer in Southern Louisiana; support services for epidemiologic studies of lung cancer in communities with non-ferrous smelters; an epidemiologic study of the incidence of cancer as related to industrial emissions in the heavily industrialized parts of Contra Costa County in California; an environmental data base for New Jersey to be used in epidemiological studies; an etiologic study of respiratory cancer in coastal Texas; and completion of the NCI/NCHS cooperative study of 1972 mortality data. (no Refs)

47. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

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Mutat Res; 87(2):191-210 1981

The development of bacterial genetic tests and their potential value for qualitative detection and quantitative potency ranking purposes are reviewed. The development of bacterial test systems is described. The most widely accepted bacterial test system possesses a combination of induced histidine auxotrophs of Salmonella in a plate assay. Most systematic comparative studies on carcinogenesis and mutagenesis have been performed in the Ames plate assay with the strains designated TA1535, TA1537, TA1538, TA98, and TA100. The qualitative correlation between mutagenicity and carcinogenicity is considered. Some chemicals are active in several different bacterial systems while others are mutagenic only in one or a few specific systems. Examples of tumor incidence enhancing chemicals in experimental animals and/or humans with no detectable or inconclusive mutagenic activity in bacterial systems and some bacterial mutagens with no evidence for or no sufficient data on animal carcinogenicity are described. Bacterial mutagenicity tests may be useful in predicting tumor-initiating potency in three instances: direct extrapolation from in vitro bacterial data obtained by standard procedures, indirect extrapolation from in vitro bacterial data obtained with representative genetic endpoints and backgrounds on the basis of correction according to extrapolation factors determined from quantitative comparative mutagenicity studies in prokaryotic and eukaryotic model organisms, and extrapolations from host-mediated assays performed with indicator microorganisms present in target organs of animals treated at practical exposure concentrations. Future prospects for bacterial test systems in mutagenicity and carcinogenicity testing are described. (153 Refs)

48. TOXICOLOGICAL CONSIDERATIONS FOR THE MEDICINAL CHEMIST.

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Med Res Rev; 1(4):337-372 1981

Toxicological considerations in the development of new drugs are reviewed. Expanding knowledge of drug metabolism and toxicology allows better direction of research into those compounds having the best chance of passing biological tests. One apparent mechanism of chemical carcinogenesis is attack by electrophilic molecules on DNA, nuclear proteins, or other cell components. A second mechanism is the induction of enzyme systems, particularly cytochrome P450 by a compound or its metabolites. Other toxicological problems include phospholipidosis, blood dyscrasias, effects on liver function, dermatological problems, hearing loss, and lupus syndrome. All of these should be considered in proposing new drugs for testing. A drug should have sufficient reversible toxicity to produce the desired effect without producing permanent damage to the patient. Quantitative structure-activity relationships and empirical approaches are reviewed. Structure-toxicity relationships of specific compounds are presented. In vivo transformation of drugs is discussed. (117 Refs)

49. ON THE CONCEPT OF THRESHOLD.

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Am Ind Hyg Assoc J; 42(11):763-770 1981

Application of threshold limit values (TLVs) to chemical substances found in workroom air which cause cancer, mutations, or defects in fetal development is discussed. Definitions (eg, critical and lethal concentrations for cells, critical organ concentrations, critical and subcritical effects, dose-effect relationships) supporting the concept of a threshold effect for metals are presented. Classification of carcinogenic chemicals into genotoxic, epigenetic, or promoter categories may be useful in establishing TLVs for exposed workers. The need to identify hypersusceptible workers and use of biological limit values in health surveillance are discussed. (19 Refs)

50. RADIATION EQUIVALENCY OF ENVIRONMENTAL CARCINOGENS: ASSAY SPECIFICITY (MEETING ABSTRACT).

Stevens RH, Cole DA
Department of Radiology, University of Iowa, Iowa City, IA, 52242
Clin Chem; 27(6):1066 1981

A major health concern for any new drug or chemical introduced in our population is its potential for inducing cancer. The presently utilized National Cancer Institute bioassay for carcinogenicity requires between two to four yr of continuous animal maintenance prior to tissue analysis and costs ranging anywhere from 300,000-500,000 dollars per substance. We have recently developed an in vivo assay designed to overcome these deficiencies based upon the induction of antitumor cell-mediated immunity (CMI) upon exposure to carcinogens compared with the levels brought about by exposure of only the hypoxic ileum and jejunum to x-rays. This allows mutagenicity/carcinogenicity to be expressed in terms of moles/rad. The procedure involves determining the increased injury to cultured x-ray induced small bowel adenocarcinoma cells as reflected in increased release of their radioiodinated membrane proteins brought about by peripheral blood lymphoid cells (PBLC) obtained from exposed rats. The present study was undertaken to establish the specificity for such measurements. The findings indicate that cytotoxic PBLC to the intestinal cancer tissues that were induced by x-rays and chemicals were not induced by nonspecific forms of injury (radiation or surgery), substances inducing cancer in other than gastrointestinal tissues (asbestos induced mesothelioma) or spontaneously arising tumors (breast or prostate). Conclusions from the study are that immunological measurements can be utilized to readily determine the mutagenicity/carcinogenicity potential of a drug. (1 Ref)

51. ENVIRONMENTAL RISKS IN HANDLING INJECTABLE ANTINEOPLASTIC AGENTS (MEETING ABSTRA CT).

Dana WJ

No affiliation given

Oncology Nursing Conference III, September 9-11, 1981, Houston, Texas. University of Texas System Cancer Center M.D. Anderson Hospital and Tumor Institute 62 pp., 1981.

With the increasing use of cancer chemotherapeutic agents, concern is being expressed regarding potential risks in handling these medications. Antineoplastic agents are known to be cancer causing agents as well, but only limited studies exist which address possible occupational hazards to health professionals involved in the preparation and administration of these products. The cancer causing risk of the these agents is likely related to the observations that some of these drugs are (a) carcinogens in laboratory animals, (b) mutagenic to cells in culture and bacterial test systems, and (c) capable of inducing chromosomal aberrations and breaks in vitro and in vivo. Further studies are needed to more specifically identify the carcinogenic and mutagenic risks and to enable practical guidelines to be developed for handling such agents. (no Refs)

52. THE TROUBLED TOXICOLOGIST.

Dayan AD

Dept. Pathology, Wellcome Res. Lab., Langley Court, Beckenham, Kent BR3 3BS, England

Trends Pharmacol Sci; 2(11):I,II,IV,V 1981

While pure toxicology is a defined field, many problems are associated with industrial toxicology. Principles and regulation of toxicity testing are discussed. Various types of toxicity testing (including tests for screening, teratology, fertility, carcinogenicity, and mutagenicity) are tabulated in relation to purpose, techniques, predictive value, and relative effort expended in the tests. (9 Refs)

53. DISTINCT REGULATORY CONSEQUENCES REQUIRED FOR GENOTOXIC CARCINOGENS AND PROMOTING AGENTS (MEETING ABSTRACT).

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We have classified chemical carcinogens into two broad classes, genotoxic and epigenetic carcinogens, subdivided in turn into eight subclasses. The mechanisms of each subclass need to be established in detail to provide the basis for rational regulatory actions applied to protect man effectively, efficiently, and economically. Genotoxic carcinogens are generally conceived to be electrophilic compounds reacting with critical cellular macromolecules, especially DNA. Unless such DNA is competently repaired, the damage can be converted into an irreversible mutation during replication. Multiplication of cells with such abnormal DNA leads to progeny bearing the neoplastic genome which can, through further infidelity in DNA synthesis, progress to more advanced neoplastic states. Conceptually, therefore, the effect of genotoxic carcinogens leads to irreversible changes, even though dose response curves do seem to indicate the existence of a practical, albeit not theoretical, thresholds. Epigenetic carcinogens operate by diverse mechanisms, sometimes highly specific as regards species, strain and tissue activity. In many instances, one mode of action is the control of the rate of cell multiplication through mechanisms to be established further. This action is highly dose dependent and is reversible. Thus, there is a time and dose threshold for such substances. Evidently, regulatory stances for such compounds should be quite different from those applicable to genotoxic carcinogens. We have devised a systematic sequence of tests to distinguish between these two major categories of carcinogens, which, when used properly, yields a data base appropriate for scientifically sound regulatory actions. (no Refs)

54. REGULATING TUMOR PROMOTERS: THE INTERACTION OF SCIENCE AND POLITICS (MEETING ABSTRACT).

Williams JR
The George Washington University, Washington, DC
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Tumor promoters, as other carcinogens, present a potential human health hazard. The real extent of that hazard is unknown. The process by which resources and regulatory attention are directed toward tumor promoters is dependent upon scientific, political and economic factors. Of paramount importance in the interaction of these factors is the selection of particular biological tests as surrogates for human response to chemicals; tests for use by chemical manufacturers, or for regulatory purpose by federal agencies. This selection of tests, in turn, depends upon the degree to which a demonstrable consensus exists that the biology of a test portrays, at least to an appreciable extent, the pathology of concern, and/or that the test has predictive value as demonstrated by a verified data base. Political factors which impinge on this selection include the cost of the test, the availability of testing resources, the consideration of particular chemicals of economic or symbolic value, and the combination of factors which produce the posturings both of the regulated attitude of federal agencies. Unless there is better definition of the essential molecular and cellular nature of cancer promotion, predictable by an inexpensive test, it is most unlikely that a meaningful screening of new or old chemicals for promotion will take place. In the absence of a scientific consensus for a methodology for evaluating promoters in the long-term whole animal bioassay, it is unlikely that commercial chemicals will be regulated to any extent based on a cancer-promoting activity. (no Refs)

55. AN OVERVIEW OF CURRENT EFFORTS IN SHORT-TERM CARCINOGEN TESTING (MEETING ABSTRACT).

Milman HA, Hurley PM, Auletta A
U.S. Environmental Protection Agency, Washington, DC
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Scientists in the Health and Environmental Review Division (HERD), Office of Toxic Substances of the US Environmental Protection Agency, are examining the feasibility of expanding efforts in short-term carcinogen testing. Three areas for consideration have been defined. These are (1) short-term in vitro tests; (2) short-term in vivo tests; and (3) tumor makers. HERD's current efforts in short-term in vitro testing are exemplified by the Gene-Tox program. Through a comprehensive system of committees and reviews, the published literature on eukaryotic and prokaryotic in vitro and in vivo test systems is being examined and analyzed. The suitability of utilizing the various systems in a test battery to identify potential chemical mutagens and carcinogens will be ascertained. Data base analyses of short-term in vivo tests (limited bioassays) and tumor markers are currently being conducted. The published literature is being evaluated and limited bioassays and tumor markers are being identified. Correlations will be made between results obtained from these tests and epidemiological information and/or long-term animal bioassays. The attributes and deficiencies of each test or marker will be examined. Further testing, development, or validation needs will be outlined. The aim is to attempt to expand the pre-chronic test battery for carcinogenicity in order to provide sufficient information for regulatory decision-making. (no Refs)

56. INDUCTION OF SKIN PAPILLOMAS IN THE SENCAR MOUSE AS A TIER 2 CARCINOGENESIS BIOASSAY (MEETING ABSTRACT).

Bull RJ, Robinson M, Glas J, Cmehil D, Orthoefer J
Health Effects Research Laboratory, Cincinnati, OH, 45268
Toxicologist; 1(1):129 1981

The Toxic Substances Control Act mandates the testing of industrial chemicals for which insufficient evidence of safety exists. One of the more critical areas in chemical carcinogenesis testing is a dependable approach to confirmatory tests (tier 2) of identifed positives at a screening level (tier 1). The present work was undertaken as part of a systematic evaluation of a series of short-term in vitro and in vivo tests which possess properties thought desirable for tier 2 testing. Experiments were designed to determine whether the mouse skin responds to initiating doses of carcinogens selected from the major carcinogen classes administered by four routes, oral, ip, sc and topical. Experiments to date include testing of diethylnitrosamine, urethane, benzene, benzo(a)pyrene, dimethylbenzanthracene (D MBA), aflatoxin B1, methylmethane sulfonate, azobenzene, FANFT and lead acetate. Two wk following application of the initiating doses of each carcinogen a 20 wk promotion schedule involving the application of 1 ug of 12-O-tetradecanoyl phorbol-13-acetate (TPA) was initiated. On the basis of preliminary data it is apparent that papilloma development in response to chemical carcinogens varies with route of exposure. For example, it is apparent that the response to urethane administered po exceeds that observed by the topical route by 3-fold. Conversely, the response of the mouse skin to benzo(a)pyrene is more than 10-fold by the topical vs systemic routes of exposure. Route specific responses to DMBA, benzene, diethylnitrosamine and aflatoxin B1 are also apparent. These results suggest that consideration be given to employing more than one route of exposure in testing of chemicals using the mouse skin initiation/promotion system. (no Refs)

57. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS

Microbiological Associates, Bethesda, MD, 20816

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 Cl 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

58. EFFECTS OF CARCINOGENS, MUTAGENS, AND TERATOGENS ON NON-HUMAN SPECIES-AQUATIC ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP

United States Environmental Protection Agency, Gulf Breeze, FL

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Aquatic systems and organisms are under both laboratory and field study in order to develop indicator, screening, and modeling capabilities for detection and evaluation of risks of carcinogens, mutagens, and teratogens. In the third yr of the program, several advances were made in the development of minnow (liver lesions via benzidine and aflatoxin exposures), rainbow trout (liver tumors via benzo(a)pyrene (B(a)P) exposures), and freshwater catfish (papillomatous-like lesions via chlorinated effluent exposures). A novel approach has shown that tiger salamanders may be good biochemical and histologic indicators of the presence of certain carcinogens (polycyclic aromatic hydrocarbons-PAH's). The skin and liver tissues of the salamanders revealed induced enzyme activity following exposure to the PAH, perylene. Considerable field monitoring work on mollusks and carcinogenic PAH's along the coast of Oregon has revealed a positive correlation between prevalence of cellular proliferation disorders in shellfish and higher concentrations of certain PAH's in natural water. Emphasis in biochemistry for the last yr has been directed mostly toward the elucidation of the metabolisms of the mixed-function oxidases in marine organisms. From continuing work on the mullet (Mugil cephalus), we have found that benzo(a)pyrene is converted mainly to 3-hydroxybenzo(a)pyrene, 9-hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-dihydroxydiols of B(a)P, in in vitro systems containing liver microsomes from Aroclor 1254-treated mullet. Other metabolites such as diones of B(a)P and probably tri- and tetraols have also been produced. We have also developed a procedure for the epoxide hydrolase enzyme system in order to determine the role of this enzyme on the metabolism of the polyaromatic hydrocarbons. These studies continue to reveal that fish have similar metabolic pathways to mammals for disposition of certain carcinogens. (no Refs)

59. CARCINOGENESIS STUDIES USING CULTURED HUMAN EPITHELIAL TISSUES AND CELLS (MEETING ABSTRACT).

Harris C, Autrup H

Human Tissue Study Section, National Cancer Institute, Bethesda, MD, 20205

Symposium on Host Factors in Human Carcinogenesis, June 8-11, 1981, Cape Sunion, Greece International Agency for Research on Cancer; 1981

Initial studies have focused on the balance between the activation and the deactivation of chemical procarcinogens and the identification of carcinogen-DNA adducts. Using the formation of adducts as a putative measure of this metabolic balance, representative procarcinogens from diverse chemical classes, ie, polynuclear aromatic hydrocarbons, N-nitrosamines, mycotoxin and hydrazines, have been investigated in cultured human bronchus, colon, pancreatic duct and esophagus. In general, the metabolic pathways and the carcinogen-DNA adducts are each qualitatively similar among people and also among outbred animal species, however, wide quantitative differences (50-to 150-fold) have been found by us and independently by other investigators. Wide differences in biological response are also found in human tissue- and cell-mediated mammalian mutagenesis assays. The occurrence of carcinogen-DNA adducts in exposed human populations and the relationship between such adducts and the mechanism(s) of carcinogenesis are two current areas of research interest. The recent development of specific and highly sensitive enzyme immunoassays for the quantitative measurement of carcinogen-DNA adducts in human cells should aid efforts in epidemiology of high cancer risk populations and in the molecular biology of carcinogen-gene interactions. (no Refs)

60. 32P-LABELING TEST FOR DNA DAMAGE.

Randerath K, Reddy MV, Gupta RC

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Proc Natl Acad Sci USA; 78(10):6126-6129 1981

Covalent adducts formed by the reaction of DNA with chemical carcinogens and mutagens may be detected by a 32P-labeling test. DNA preparations exposed to chemicals known to bind covalently to DNA [N-methyl-N-nitrosourea, dimethyl sulfate, formaldehyde, beta-propiolactone, propylene oxide, streptozotocin, nitrogen mustard, and 1,3-bis(2-chloroethyl)-1-nitrosourea] were digested to a mixture of deoxynucleoside 3'-monophosphates by incubation with micrococcal endonuclease (EC 3.1.31.1) and spleen exonuclease (EC 3.1.16.1). The digests were treated with [gamma-32P]ATP and T4 polynucleotide kinase (ATP:5'-dephosphopolynucleotide 5'-phosphotransferase, EC 2.7.1.78) to convert the monophosphates to 5'-32P-labeled deoxynucleoside 3',5'-bis-phosphates. These compounds were then separated on polyethyleneimine-cellulose thin layers in ammonium formate and ammonium sulfate soln. Autoradiograms of the chromatograms obtained by this high-resolution procedure showed the presence of nucleotides derived from chemically altered, as well as normal, DNA constituents. Maps from DNA exposed to any of the chemicals used exhibited a spot pattern typical for the particular chemical. This method detected a single adduct in 10(5) DNA nucleotides without requiring that the compound under investigation be radioactive and thus provides a useful test to screen chemicals for their capacity to damage DNA by covalent binding. (Author abstract) (41 Refs)

61. AUTORADIOGRAPHIC STUDY OF DNA REPAIR SYNTHESIS IN TRACHEAL EPITHELIUM IN ORGAN CULTURE, WITH SPECIAL REFERENCE TO DNA REPAIR LEVELS AND SPECIES DIFFERENCES (MEETING ABSTRACT).

Ishikawa T, Takayama S
Department of Experimental Pathology, Cancer Institute, Tokyo, Japan
Symposium on Host Factors in Human Carciuogenesis, June 8-11, 1981, Cape Sunion, Greece International Agency for Research on Cancer; 1981

Small sections of trachea or bronchi in organ cultures were treated with various carcinogens plus tritiated thymidine. In this system, unscheduled DNA synthesis (UDS) could be clearly demonstrated over the nuclei of cells treated with carcinogens. This autoradiographic method is suitable for quantitative measurement of UDS in respiratory cells in conditions mimicking those in vivo. To test the validity of this system, cultures of rat tracheal epithelium were used to detect the ability of about 50 chemicals to induce UDS. These results suggest that this system should be useful for screening environmental chemicals suspected of damaging DNA of the respiratory organs in relation to lung carcinogenesis. For the study of DNA repair levels and species differences, pieces of trachea from six species (mice, rats, hamsters, guinea-pigs, pigs and cows - all young adult males) were treated with 3 carcinogens (4-nitroquinoline 1-oxide, methyl methanesulfonate and ethylnitrosourea) in the short-term organ culture. We found that the carcinogen-induced DNA repair levels differed considerably from species to species. However, the relative efficiency of DNA repair of the six species tested differed from one carcinogen to another. Our observations suggest that the excision-repair efficiency may depend both on the cell type and the type of DNA repair efficiency in differences in carcinogenesis. (no Refs)

62. CHARACTERIZATION OF DNA REPAIR ELICITED BY CARCINOGENS AND DRUGS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

McQueen CA, Williams GM
(c/o Williams), American Health Foundation, 1 Dana Road, Valhalla, NY, 10595
J Toxicol Environ Health; 8(3):463-477 1981

Autoradiographic unscheduled DNA synthesis measured in the hepatocyte primary culture/DNA repair test after exposure to chemical carcinogens was characterized. Replicated and nonreplicated hepatocyte DNA was separated by CsCl gradient centrifugation. Uptake of 3H-thymidine into nonreplicated DNA was seen after exposure of hepatocytes to the activation-independent carcinogen methyl methanesulfonate or the activation-dependent carcinogen N-2-acetylaminofluorene, but not with fluorene, a noncarcinogen. N-4-acetylaminofluorene, a mutagen with uncertain carcinogenicity, also elicited DNA repair. Density gradient centrifugation allowed the detection of DNA repair in hepatocytes following exposure to the antihistamines pyrilamine maleate and tripelennamine HCl. Methapyrilene did not elicit repair. (44 Refs)

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Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

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3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

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ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

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Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

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10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

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13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull, 25(3):125-146 1981

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APRIL, 1982

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IN VIVO TESTS FOR MUTAGENICITY

1. AN APPROACH TOWARDS THE STANDARDIZATION OF THE MAMMALIAN SPOT TEST.

Neuhauser-Klaus A
Institut fur Genetik, Abteilung fur Saugetiergenetik, Gesellschaft fur Strahlen- und Umweltforschung, Post Oberschleissheim, D-8042 Neuherberg, W. Germany

Arch Toxicol; 48(4):229-243 1981

The mammalian spot test has recently been demonstrated as a promising method for the detection of somatic mutations induced by chemicals. The results reported here are our effort toward the validation and standardization of this test system

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for mutagenicity testing. (T x HT)F1 embryos, heterozygous for the recessive coat color alleles ln, pa, b, cch, p, d, and pe were exposed in utero to a single dose of the test compound between day 8 and 11 post conception. To compare the sensitivities of different genotypes of embryos an additional experiment was carried out with (C57BL/6JHan x T)F1 embryos, which are heterozygous for b, cch, p, and d. The offspring were screened for the presence of color spots at the age of 12-14 days and at weaning. The chemical mutagens used in the present experiment were mitomycin C (MC), methyl methanesulfonate (MMS), and procarbazine. The lowest doses tested in these experiments which induced coat color spots (presumed somatic mutations) were 1 mg/kg MC, 50 mg/kg MMS, and 50 mg/kg procarbazine, when the females were treated on Day 9 of pregnancy. The frequency of white midventral spots (WMVS), which are caused by an inactivation of melanocyte precursor cells, was increased in the higher dose groups of MC and procarbazine. These doses also reduced the av litter size and caused malformations. The type of malformations depended on the day of treatment. The data obtained with 50 mg/kg procarbazine indicate comparable sensitivities of the two genotypes (T x HT)F1 and (C57BL/6JHan x T)F1. The lowest doubling doses calculated for somatic mutations were 0.3 mg/kg MC, 6.6 mg/kg MMS and 11 mg/kg procarbazine. For germinal gene mutations they were 0.6 mg/kg MC, 1.2 mg/kg MMS and 34 mg/kg procarbazine. The comparison between the expected and observed distribution of coat color spots between the head and body of the mice supports randomness of distribution. Further analysis of the data revealed that the scoring of spots only in the dorsal and lateral regions does not alter the sensitivity of the test. Thereby one can avoid any ambiguity arising from the distribution of midventral white gray and light gray spots. (Author abstract) (26 Refs)

2. EFFECTS IN THE MAMMALIAN SPOT TEST: CYCLAMATE VERSUS SACCHARIN.

Fahrig R

Institut fur Toxikologie der Eberhard-Karls-Universitat, Wilhemstr. 56, D-7400 Tubingen, W. Germany

Mutat Res; 103(1):43-47 1982

Effects of cyclamate and saccharin (SH) in pigment cells of mouse embryos were compared using the mammalian spot test, an in vivo system for detection of genetic alterations including gene mutations. Embryos of the cross C57Bl/6JHan x T stock, heterozygous for four different recessive coat-color genes, were treated in utero on day 10 post-conception. At this time approx 200 pigment precursor cells are available. Treatment consisted of the cyclamate metabolite cyclohexylamine (CHA; 100-200 mg/kg ip), SH (1 g/kg ip), or the SH impurity orthotoluene sulfonamide (OTS; 1 g/kg po in tragacanth). Results indicated CHA was a weak mutagen, with 5/7 experiments giving positive results (8 spots of genetic relevance among 1,332 mice compared to 1 spot in 1,249 controls). With OTS, at least one color spot was observed in each of three experiments, only one considered significant. Hence, classification of OTS as mutagenic or non-mutagenic is not possible. SH should be considered non-mutagenic because the one color spot among 701 mice did not differ significantly from the spontaneous frequency. On the basis of the mammalian spot test alone, cyclamate must be considered potentially more dangerous than SH if the SH preparation used is free of impurities like OTS. (15 Refs)

3. INVESTIGATIONS ON RADIOSENSITIVE AND RADIORESISTANT POPULATIONS OF DROSOPHILA MELANOGASTER. XIII. EFFECTS OF RADIORESISTANT MUTANTS (RAR) ON CHEMICAL (EMS) MUTAGENESIS.

Nothel H, Strese B

Institut fur Genetik, Freie Universitat Berlin, Berlin-Dahlem, W. Germany

Mutat Res; 103(1):87-90 1982

After treatment with ethyl methanesulfonate (EMS), treated Drosophila melanogaster males were mass mated to Basc females and treated D melanogaster females to males carrying Ys In(1)EN car f In(1)dl49 v y-YL/0. Sex-linked recessive lethals were scored as percentage of X-chromosomes tested, after treatment of various germ-cell stages of +K (normals), ROI/0, rar-3, and ROI/40 with EMS in various forms of application (injection or fed). Mutation frequencies indicated normal efficiency of EMS injection. High mutational yields from mature oocytes indicated a reasonable uptake of EMS after feeding and confirmed the marked sensitivity of stage-14 oocytes compared with stage-7 and younger oocytes. The low sensitivity of immature oocytes to EMS makes comparison between genotypes somewhat difficult. The system of relative radioresistance, which has evolved under the irradiation conditions of the populations ROI and ROI/4, is not based on specific radiobiological processes but involves more general pathways of mutagenesis. (13 Refs)

4. PARAMETRIC STATISTICAL METHODS AND SAMPLE SIZE CONSIDERATIONS FOR DOMINANT LETHAL EXPERIMENTS: THE USE OF CLUSTERING TO ACHIEVE APPROXIMATE NORMALITY.

Whorton EB

Dept. Preventive Medicine, Univ. Texas Medical Branch, 123 Keiller Bldg, Galveston, TX, 7750

Teratogenesis Carcinog Mutagen; 1(4):353-360 1981

A methodology for statistical analysis of results obtained in the dominant lethal assay of mutagenic potential is presented. This method incorporates a data clustering scheme to achieve desirable distributional properties of measured variables in order to allow the use of analysis of variance and relate parametric testing procedures. (19 Refs)

5. AN EVALUATION OF THE DROSOPHILA ZESTE SOMATIC EYE MUTATION TEST FOR THE DETECTION OF GENOTOXIC AZO DYES AND AN AROMATIC AMINE.

Edwards CN, Combes RD

Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, Hants, P01 2DY, England

Mutat Res; 84(1):221-226 1981

As part of a program for the assessment of genotoxicity of two currently United Kingdom-listed amino-azo food colors Brown FK and Red 2G and its delisted structural analogue Red 10B, the zeste somatic eye mutation system was used as a potentially sensitive single generation assay requiring further validation as an alternative to the sex-linked recessive lethal assay. A modification facilitating the use of the test with dyes and an evaluation of its sensitivity to 2-acetylaminofluorene (2-AAF) and o-aminoazotoluene was also undertaken. The zeste somatic eye system was incapable of detecting the activity of 2-AAF. (28 Refs)

6. RAPID INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE-RICH INTRAEPITHELIAL CLONES IN 7,12-DIMETHYLBENZ(A)ANTHRACENE-TREATED HAMSTER BUCCAL POUCH.

Solt DB, Shklar G
Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA, 02115
Cancer Res; 42(1):285-291 1982

Individual gamma-glutamyl transpeptidase (GGT)-stained cells and cell doublets were rapidly induced in the epithelium of hamster buccal pouch treated with biweekly topical applications of 0.5% 7,12-dimethylbenz(a)anthracene (DMBA) in mineral oil. The cells were detected histochemically in whole mounts of pouch epithelium harvested as early as 3 days after the first application of this carcinogen. During 3 consecutive wk of DMBA treatment, progressively larger GGT-stained epithelial cell populations (plaques) up to 0.5 mm in diameter were encountered. Similar GGT-stained lesions were not detected in whole mounts of untreated epithelium and were rarely seen in GGT-stained whole mounts prepared from mineral oil-treated pouch epithelium. In an experiment designed to assess the stability of the GGT-staining pattern, very few plaques could be detected 12 wk after a 3-wk regimen of six DMBA applications. However, data are presented suggesting that a brief series of three DMBA applications reinduced GGT histochemical activity in occult intraepithelial plaques, which had lost enzyme activity but had persisted over an 11-wk treatment-free interval. The clonal nature of the GGT-stained plaques and their apparent ability to persist in an occult form for several wk or mo lend further support to the hypothesis that these carcinogen-altered cell populations may be potential precursors for the development of squamous epithelial neoplasia. (Author abstract) (40 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

7. THE RELATIONSHIP BETWEEN THE CARCINOGENICITY AND MUTAGENICITY OF NITROSAMINES IN A HEPATOCYTE-MEDIATED MUTAGENICITY ASSAY.

Jones CA, Marlino PJ, Lijinsky W, Huberman E
(c/o Huberman) Div. Biological and Medical Res., Argonne Natl. Lab., 9700 S. Cass Ave., Argonne, Il, 60439
Carcinogenesis; 2(10):1075-1077 1981

The hepatocyte-mediated mammalian cell mutagenesis assay was used to determine the mutagenic activity of 26 nitrosamines for which a carcinogenic potency could also be established. Mutagenesis was measured in Chinese hamster V79 cells cocultivated with primary rat hepatocytes, which are capable of activating nitrosamines. Resistance to ouabain and to 6-thioguanine served as genetic markers. Carcinogenicity data were obtained from experiments in which groups of male and female Fischer rats were treated with nitrosamines po for 50 wk. A linear relationship between carcinogenicity and mutagenicity was established ($p = 0.0001$). The correlation coefficients at the 6-thioguanine and the ouabain markers were 0.85 and 0.66, respectively. This study demonstrates that the use of intact hepatocytes to activate nitrosamines, coupled with appropriate mammalian target cells to indicate genetic damage, represents a useful system for both detecting and establishing the mutagenicity of a series of nitrosamines in a manner corresponding to the carcinogenic potency produced by the same chemicals in vivo. (24 Refs)

8. CYTOTOXIC AND MUTAGENIC EFFECTS OF STERIGMATOCYSTIN ON CULTURED CHINESE HAMSTER CELLS.

Noda K, Umeda M, Ueno Y
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho, Minami-ku, Yokohama 232, Japan
Carcinogenesis; 2(10):945-949 1981

Cytotoxicity and mutagenicity of sterigmatocystin (STC) on cultured Chinese hamster cells were investigated in the presence and absence of a metabolic activation system. STC, when applied directly to V79 cells, was cytotoxic and induced 8-azaguanine-resistant mutations in a dose- and time-dependent manner. Effects of STC were enhanced markedly by 1%, 5%, or 20% S15 (polychlorinated biphenyl-induced rat liver microsomes) and other cofactors. In the presence of 1% S15, STC concentration required to induce cytotoxicity was approx 20x less than that required when S15 was applied directly; 1% STC was more cytotoxic and more mutagenic than either 5% or 20% STC. Analysis on the basis of equitoxic levels demonstrated that there was little difference in the degree of mutagenicity induced by direct treatment with STC and treatment with STC in the presence of S15. The effects of STC were enhanced in proportion to the duration of the treatment period. Treatment for shorter periods, however, was more effective than that for longer periods. The decreased effectivness was not attributable to instability of STC. (21 Refs)

9. CYTOTOXICITY AND MUTAGENICITY OF DINITROTOLUENES IN CHINESE HAMSTER OVARY CELLS.

Abernethy DJ, Couch DB
(c/o Couch) Dept. Genetic Toxicology, Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709
Mutat Res; 103(1):53-59 1982

Technical grade dinitrotoluene (DNT), a mixture composed predominantly of 2,4-and 2,6-DNT but containing lesser amounts of 2,3-, 2,5-, 3,4-, and 3,5-DNT, was tested for mutagenicity using the Chinese Hamster Ovary/Hypoxanthine-Guanine Phosphoribosyl Transferase system. Induction of mutation to 6-thioguanine (TG) resistance was tested in the presence and absence of microsomal preparations (PMS) from rats pretreated with the mixed function oxidase inducer Aroclor 1254. Marked differences in isomeric cytotoxicity were observed. However, neither technical grade DNT nor any of the purified isomers resulted in a significant increase in the TG-resistant fraction of surviving cells with or without PMS. (19 Refs)

10. CYTOGENETIC ANALYSIS OF THE L5178Y/TK+/- [LEADS TO]TK-/- MOUSE LYMPHOMA MUTAGENESIS ASSAY SYSTEM.

Hozier J, Sawyer J, Moore M, Howard B, Clive D
Cytogenetics Lab., Dept. Biological Sciences, Florida Inst. Technology, Melbourne, FL, 32901
Mutat Res; 84(1):169-181 1981

The L5178Y/TK+/- mouse lymphoma cell line and its TK-/- mutants, which are used in the L5178Y/TK+/-[leads to]TK-/- mutagen assay (TKMA), are characterized. Mutagenesis in this system produces two cell types lacking thymidine kinase (TK) activity (TK-/-) types: large-colony (lambda) and small-colony (sigma) forms. The parental TK+/- heterozygote cells have a stable karyotype, characterized by the presence of normal mouse chromosomes and recognizable rearrangements. Lambda cells have essentially the same karyotype as the heterozygote cells. Sigma clones show considerable chromosome rearrangement, particularly involving one chromosome 11. Analysis of chromosome rearrangements suggests that lambda cells have lost TK activity as the result of a point mutation, while sigma cells have lost it due to chromosomal events. The TKMA evidently can detect both point mutations and chromosomal rearrangements involving the TK locus. (18 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

11. THE EFFECT OF DIMETHYLSULFOXIDE ON THE MUTAGENICITY OF THE HAIR DYE P-PHENYLENEDIAMINE.

Burnett C, Fuchs C, Corbett J, Menkart J
Clairol Res. Laboratories, Stamford, CT, 06902
Mutat Res; 103(1):1-4 1982

Mutagenicity of p-phenylenediamine was examined in the Ames test. Choice of solvents and tight controls were shown to be important. Aqueous and fresh soln in dimethylsulfoxide were non-mutagenic; however, on standing at room temperature for 4 hr, the latter soln became highly active. (11 Refs)

12. MUTAGENICITY PATTERNS RESULTING FROM THE REACTION OF NITRITE WITH ICR-170.

de Flora S, Zanacchi P, Camoirano A, Bennicelli C
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Mutat Res; 103(1):13-17 1982

ICR-170, 2-methoxy-6-chloro-9-(3-[ethyl-2-chloroethyl] aminopropylamino) acridine.2HCl reacted with nitrite in an acidic environment to form a mutagenic derivative. Suitable soln of sodium nitrite were preincubated, either separately or mixed together, with 5 ml of human gastric juice or 0.15 M NaCl adjusted to various pH values. After 60 min at 37 C, 1 ml of 0.2 M phosphate-buffered saline, pH 7.4, was added. The resulting mixtures (0.5 ml/plate) were assayed in the plate incorporation test using various Salmonella his- strains. All the strains except TA1535 were reverted by ICR-170. TA1537 was most sensitive, a finding typical for acridine derivatives. Mutagenicity of TA1537 and of the other positive strains (TA 1538, TA98, and TA100) was increased by rat liver S9 fractions. The metabolic effect was less pronounced than previously reported for the same compound lacking an ethyl group (ICR-191). Direct frameshift activity of ICR-170 decreased in all positive strains after its reaction with nitrite. Such an activity was replaced by an S9-requiring mutagenic response in TA1538, TA98, and TA100; the response correlated with the amounts of both ICR-170 and nitrite. The study suggests that nitrosation of ICR compounds occurs at the only site where ICR-170 and ICR-191 are different, ie, at the terminal nitrogen of the nitrogen-mustard moiety. (10 Refs)

13. SYNTHESIS AND MUTAGENIC ACTIVITY OF ALKYL DERIVATIVES OF 2-AMINO-9H-PYRIDO[2,3-B]INDOLE.

Matsumoto T, Yoshida D, Tomita H
Central Res. Inst., The Japan Tobacco and Salt Public Corporation, 6-2, Umegaoka, Midori-ku, Yokohama 227, Japan
Agric Biol Chem; 45(9):2031-2035 1981

Synthesis and mutagenic activity of 2-amino-3-methyl-9H-pyrido[2,3-b]indole (MeAC) and other alkyl derivatives of 2-amino-9H-pyrido[2,3-b]indole (AC) were investigated; identification of 2-amino-3-ethyl-9H-pyrido[2,3-b]indole (EtAC) in the pyrolysate of soybean globulin is reported. Ames tests and rec-assays gave similar results with MeAC and AC, showing substantially the same mutagenic activity as MeAC and EtAC obtained from soybean globulin. An increase in number of carbons in the alkyl group was accompanied by a decrease in mutagenic activity. Activation of the C-2 amino group by liver-homogenate may have been hindered sterically by a neighboring substituent, as possibly was the binding of DNA and the activated compound. (11 Refs)

14. MUTAGENICITY OF OIL-SHALE ASH.

Whong WZ, Sorenson WG, Elliott JA, Stewart J, Simpson J, Piacitelli L, McCawley M, Ong T
Div. Respiratory Disease Studies, Natl. Inst. for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505
Mutat Res; 103(1):5-12 1982

Three oil shale samples were analyzed for mutagenicity in four test systems after extraction with solvents. In Salmonella typhimurium, extracts were highly mutagenic with Ames his reversion and ara-resistant systems; mutation induction was independent of metabolic activation and was of the frameshift type. The extracts showed substantial killing effect, but they failed to induce ad-3 reversion in Neurospora crassa, gene conversion and mitotic crossing-over in Saccharomyces cerevisiae, or TGr mutation in cultured CHO cells. (14 Refs)

15. MUTAGENICITY OF GLYCEROL CHLOROHYDRINES AND OF THEIR ESTERS WITH HIGHER FATTY ACIDS PRESENT IN PROTEIN HYDROLYSATES.

Silhankova L, Smid F, Cerna M, Davidek J, Velisek J
Dept. Biochemistry and Microbiology, Inst. Chemical Technology, 166 28 Prague 6, Czechoslovakia
Mutat Res; 103(1):77-81 1982

Mutagenicity of the glycerol chlorohydrines 3-chloro-1,2-propanediol (3CP) and 1,3-dichloro-2-propanol (1,3DP), and of their esters with palmitic and oleic acids, was tested with strains of Salmonella typhimurium and Escherichia coli. 3CP and 1,3DP caused base substitutions in S typhimurium TA1535 with and without metabolic activation. Metabolic activation in vitro with S9 mix did not influence the mutagenic effect of non-toxic concentrations of the glycerol chlorohydrines, but it led to a strong increase in the amount of mutants with those chlorohydrine concentrations causing strong suppression of background growth without metabolic activation. Difference in the growth of wild-type and repair-deficient strains of E coli was observed only for 1,3DP with S9 mix. Esters of both 3CP and 1,3DP with fatty acids had smaller mutagenic effects than unesterified compounds. (16 Refs)

16. CONVERSION OF CHLORINATED NITROBIPHENYL ETHERS AND THEIR DERIVATIVES TO MUTAGENS BY WHITE-SPOTTED CHAR, SALVELINUS LEUCOMAENIS, LIVER HOMOGENATE.

Miyauchi M, Takagi M
Lab. Food Hygiene, Faculty of Fisheries, Hokkaido Univ., Hakodate 041, Japan
Bull Jpn Soc Sci Fish; 47(2):243-250 1981

Mutations were induced by p-nitrobiphenyl ether, its chlorinated forms, and their nitroso derivatives in a Salmonella typhimurium assay without liver homogenate. Liver homogenate from the white-spotted char increased mutagenicity of the compounds slightly and greatly increased the mutagenicity of amino derivatives. (23 Refs)

CYTOGENETIC TESTS

17. CYTOGENETIC STUDY OF WORKERS EXPOSED TO METHYL-PARATHION.

de Cassia Stocco R, Becak W, Gaeta R, Rabello-Gay MN
Servico de Genetica, Instituto Butantan, Caixa Postal 65, Sao Paulo, Brazil
Mutat Res; 103(1):71-76 1982

Cell aberrations were studied in a group of 15 subjects exposed to methyl-parathion (O,O-dimethyl-o,p-nitrophenyl phosphorothioate); subject cholinesterase levels were 75% or less of normal. Period of exposure varied from 1 wk to 7 yr, with intermittent periods of non-exposure. Controls were 13 men with 100% cholinesterase level who had not been occupationally exposed to any chemical and were of comparable age and socioeconomic status. The workers exposed to methyl-parathion did not show an increased frequency of chromosome aberrations in lymphocyte cultures compared to the non-exposed controls. Considering that methyl-parathion is often contaminated with DDT (dichloro-diphenyl trichloroethane), seven exposed and eight control subjects were randomly assayed for DDT and its principal metabolite DDE (1,1-dichloro-2,2-bis[p-chlorophenyl]ethylene). Levels of DDT in exposed individuals did not differ significantly from those of controls. While it is known that increased chromosome aberrations occur in cases of acute intoxication, chronic exposure to small doses of methyl-parathion in the work place do not seem to produce the same effect. (16 Refs)

18. THE ACTION OF TRANSITION METALS ON THE GENOTOXICITY OF SIMPLE PHENOLS, PHENOLIC ACIDS AND CINNAMIC ACIDS.

Stich HF, Rosin MP, Wu CH, Powrie WD
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 W. 10th Ave., Vancouver V5Z 1L3, Canada
Cancer Lett; 14(3):251-260 1981

The capacity of several phenolic compounds to induce chromatid breaks and exchanges in Chinese hamster ovary cells, and the modulating effect of the transition metals Cu++ and Mn++ on the clastogenicity of phenolics were examined. All dihydroxylated and trihydroxylated phenolics induced chromatid breaks and exchanges. Addition of S9 mixture or transition metals enhanced clastogenicity of some phenolics but reduced it in others. (35 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

19. EFFECT OF 1,2-DIMETHYLHYDRAZINE AND DIETHYLNITROSAMINE ON CELL REPLICATION AND UNSCHEDULED DNA SYNTHESIS IN TARGET AND NONTARGET CELL POPULATIONS IN RAT LIVER FOLLOWING CHRONIC ADMINISTRATION.

Lewis JG, Swenberg JA
(c/o Swenberg), Chemical Industry Inst. Technology, Research Triangle Park, NC, 27790
Cancer Res; 42(1):89-92 1982

Marked differences in the rates of de novo DNA synthesis and unscheduled DNA synthesis were observed in hepatocytes and nonparenchymal cells (NPC) isolated from Fischer 344 rats following in vivo exposure to 1,2-dimethylhydrazine (SDMH) or diethylnitrosamine (DEN) for 1.5, 4, 8, 16, and 28 days. Liver cells were labeled in vivo with bromodeoxyuridine and [3H]thymidine, following which, hepatocytes and NPC were separated by elutriation centrifugation. Purified DNA was then separated into fully replicated and nonreplicated DNA by ultracentrifugation in CsCl gradients. Following exposure to SDMH, the rate of de novo DNA replication in NPC was greatly increased over both control NPC and the corresponding hepatocytes for the entire time course. Unscheduled DNA synthesis was only observed in hepatocytes after exposure to SDMH. Following exposure to DEN, both cell populations exhibited changes in de novo DNA synthesis that were directly proportional to one another except at 1.5 days. Increases occurred first in hepatocytes at 1.5 days but were delayed in NPC until 4 days. Hepatocyte replication returned to control values by 28 days. Unscheduled DNA synthesis was much lower following exposure to DEN than SDMH. Therefore, SDMH, which induces hemangioendotheliomas of the liver at the dose given, induces a marked increase in cell replication in the target cell population and unscheduled DNA synthesis in the resistant cell population. DEN, which induces hepatocellular carcinoma, moderately stimulates cell replication in both liver cell populations and induces little unscheduled DNA synthesis in either population. (Author abstract) (19 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

20. ETHANOL- OR ACETONE-PRETREATMENT OF MICE STRONGLY ENHANCES THE BACTERIAL MUTAGENICITY OF DIMETHYLNITROSAMINE IN ASSAYS MEDIATED BY LIVER SUBCELLULAR FRACTION, BUT NOT IN HOST-MEDIATED ASSAYS.

Glatt H, De Balle L, Oesch F

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Carcinogenesis; 2(10):1057-1061 1981

The effect of acetone or ethanol pretreatment of mice on dimethylnitrosamine (DMN) mutagenicity in host- and liver subcellular fraction-mediated assays was investigated. Salmonella typhimurium TA 92 was used in both the in vitro S9-mediated assay and in the in vivo host-mediated assay because it was more sensitive than TA 1535, TA 100, or Escherichia coli WP2 uvrA and because it possesses an intact polysaccharide layer. Pretreatment of C57BL/6J mice with either 45 millimoles of acetone or 30-60 millimoles of ethanol per kg potentiated DMN mutagenicity in S9 mix-mediated assays. At low DMN concentrations (100 uM), greater than 100x more mutants were induced with S9 mix from acetone-treated mice than with S9 mix from controls. Ethanol had a similar, but weaker, effect. In the host-mediated assay, DMN was a potent mutagen, but this effect was not enhanced by pretreatment with either acetone or ethanol. In general, mutagenicity was slightly lower in acetone-pretreated animals than in controls. A possible explanation for the differences observed in vitro and in vivo may be that in vitro the activity of the dilute metabolizing system is limiting for the activation of DMN, whereas in vivo DMN is completely metabolized in both induced and noninduced animals. (16 Refs)

21. METABOLIC ACTIVATION OF AFLATOXIN B1 BY LIVER TISSUE FROM MALE FISCHER F344 RATS OF VARIOUS AGES.

Jayaraj A, Richardson A
Dept. Biological Sciences, Illinois State Univ., Normal, IL, 61761
Mech Ageing Dev; 17(2):163-171 1981

The effect of aging on the ability of the liver to activate chemical procarcinogens was studied using 12-, 18-, and 27-mo-old male Fischer F344 rats. The cytochrome P-450 content of the S9 and microsomal fractions of the liver decreased approx 30% between 12 and 18 mo of age. The structural conformation of cytochrome P-450 in microsomes from 12-, 18-, and 27-mo-old rats was studied using electron-spin resonance spectroscopy. An age-related decrease in the amount of cytochrome P-450 ferric iron in the liver microsomes was observed. The conversion of the chemical procarcinogen aflatoxin B1 to mutagenic compounds by the S9 and microsomal fractions of liver was measured using the Salmonella typhimurium bioassay. A 40-50% decrease in the metabolic activation of aflatoxin B1 was observed between 12 and 18 mo of age. However, the activation of aflatoxin B1 did not change after 18 mo of age. The age-related decrease in the activation of aflatoxin B1 by liver appears to be due to a decrease in the metabolic activity of the mixed-function oxidase system. (Author abstract) (27 Refs)

22. THE ACTIVATION OF AFLATOXIN B1 IN LIVER SLICES AND IN BACTERIAL MUTAGENICITY ASSAYS USING LIVERS FROM DIFFERENT SPECIES INCLUDING MAN.

Booth SC, Bosenberg H, Garner RC, Hertzog PJ, Norpoth K
(c/o Garner) Cancer Res. Unit, Univ. York, York Y01 5DD, England
Carcinogenesis; 2(10):1063-1068 1981

Activation of aflatoxin B1 (AFB1) was compared in two in vitro systems: binding to DNA in liver slices incubated with 14C- or 3H-AFB1 and in standard bacterial mutation systems using 9000 x gravity supernatant (S-9) fractions from uninduced livers for activation. The results were compared in several rodent species in an effort to correlate them with known trends in carcinogenicity. Covalent binding of 14C-AFB1 to DNA from liver slices showed the order rat greater than hamster greater than mouse. Phenobarbitone pretreatment of rats decreased binding, and binding of aflatoxin G1 (AFG1) was less than that of AFB1. These findings all were correlated with relative susceptibility to AFB1-induced hepatocarcinogenesis. An exception to this trend was the similar level of binding found in male and female rat livers. Levels of 3H-AFB1 binding to DNA in human liver biopsies ranged from 0.7-8.5 nanog AFB1/mg DNA, which was similar to the range seen in the mouse and hamster. Mutagenicity data did not correlate with carcinogenicity in relation to species differences, as the efficiencies of livers from the three species for activating AFB1 mutagenicity were hamster greater than rat greater than mouse. AFG1 mutagenicity generally was markedly less than that of AFB1 when activated by rat liver S-9. The correlation between AFB1 binding to DNA in liver slices in various rodent species and susceptibility to AFB1 hepatocarcinogenesis and its modification in the rat by phenobarbitone suggests that these differences are related to differences in metabolic activation of AFB1 to its reactive species, its subsequent detoxification, and macromolecular interaction. (30 Refs)

23. METABOLIC ACTIVATION OF A TRYPTOPHAN PYROLYSIS PRODUCT, 3-AMINO-1-METHYL-5H-PYRIDO(4,3-B)INDOLE (TRP-P-2) BY ISOLATED RAT LIVER NUCLEI.

Mita S, Yamazoe Y, Kamataki T, Kato R
Dept. Pharmacology, Sch. Medicine, Keio Univ., Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
Cancer Lett; 14(3):261-266 1981

The abilities of nuclei and microsomes to convert 3-amino-1-methyl-5H-pyrido[3,4-b]indole (Trp-P-2) to an active mutagen were compared. Nuclei from polychlorinated biphenyl or methylcholanthrene-treated rats activated Trp-P-2 and caused a greater number of revertants in the Salmonella mutation test than nuclei isolated from phenobarbitol-treated or non-treated rats. Similar pretreatment effects were observed with microsomal activation. (17 Refs)

24. ACTIVATING EFFECT OF SEVERAL ENZYME-PROTEINS ON THE MUTAGENICITY OF AMINO-THIOL COMPOUNDS.

Yamaguchi T, Yamashita Y
Dept. Food and Nutrition, Yamaguchi Women's Univ., Yamaguchi, Yamaguchi 753, Japan
Agric Biol Chem; 45(9):2157-2160 1981

Ames test mutagenicity of several amino-thiol compounds was activated with S-9 mix and with addition of pepsin, catalase, D-amino acid oxidase, or thermolysin. Activating effects continued after heating in a boiling water bath for 10 min. All enzymes but thermolysin have a liver origin. The activating effects may result not from enzymatic activities but from the chemical reaction of enzyme proteins with cysteine or penicillamine. Other enzymes had no such activating effect. (10 Refs)

COMPARATIVE TEST RESULTS

25. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

Kirkland DJ, Smith KL, Van Abbe NJ
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire HR8 1LG, England
Food Cosmet Toxicol; 19(5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform (r = 0.206). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

26. MUTATION INDUCTION AND KILLING OF PROKARYOTIC AND EUKARYOTIC CELLS BY 8-METHOXYPSORALEN, 4,5'-DIMETHYLANGELICIN, 5-METHYLANGELICIN, 4'HYDROXYMETHYL-4,5'-DIMETHYLANGELICIN.

Pani B, Babudri N, Venturini S, Tamaro M, Bordin F, Monti-Bradgadin C
Inst. Microbiology, Univ. Trieste, Trieste, Italy
Teratogenesis Carcinog Mutagen; 1(4):407-415 1981

Three newly synthesized angular furocoumarins, 4,5'-dimethylangelicin (DMA), 5-methylangelicin (5MA), and 4'-hydroxymethyl-4,5'-dimethylangelicin (OHDMA) were compared to 8-methoxypsoralen (MP), a well known linear furocoumarin with established therapeutic properties. The mutagenic and cytotoxic effects of these compounds were tested in two bacterial strains and in V79 Chinese hamster cells. With V79 cells treated with near UV and furocoumarins, MP, the only compound able to form cross-links, was the most cytotoxic, although the three angelicin derivatives also showed an appreciable cytotoxicity. Angular furocoumarins were found to be non-cytotoxic for Escherichia coli TM6 strain (WP2 uvr+/R46), while MP reduced survival by 50% after 16 min of near UV. The angelicin compounds were as cytotoxic as MP in excision-deficient E coli strain TM9 (WP2 uvrA/R46). 5MA induced more revertants than MP in uvrA strain. 3-carbethoxypsoralen induced only a small number of mutants in V79 cells. (19 Refs)

27. GENETIC EFFECTS OF MICROWAVE RADIATION IN MICE.

Goud SN, Rani MV, Reddy PP, Reddi OS, Rao MS, Saxena VK
Dept. Genetics, Osmania Univ., Hyderabad-500 007, India
Mutat Res; 103(1):39-42 1982

Male Swiss albino mice were exposed to whole body microwave radiation from a microwave diathermy unit at 2,450 megahertz, CW and at a power density of 170 milliwatts/square cm for 70 sec. Immediately after treatment, males were mated with virgin females, the females were replaced weekly for 3 wk. Females were autopsied 13 days after caging and scored for total implantations, dead implantations (early and late deaths) and live embryos. Microwave exposure significantly decreased the dominant lethal mutation fertility index in all 3 wk of matings. Post-implantation loss was enhanced significantly (p less than 0.01) in all the post-meiotic stages and was highest in the spermatid stage. Pre-implantation and total losses also increased significantly (p less than 0.01) in wk 2 and 3. The sperm abnormality assay revealed a significant increase in abnormal sperm in microwave-exposed mice. Thus, microwaves induce dominant lethal mutations in post-meiotic stages and sperm-shape abnormalities in mice. (13 Refs)

28. MUTAGENIC ACTIVITY OF ISONIAZID AND ITS METABOLITES IN DIFFERENT TEST SYSTEMS.

Menon MM, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 19(10):939-942 1981

The mutagenic activity of isoniazid (INH) and its metabolites was examined using the Ames test system employing Salmonella typhimurium strains as well as two in vivo mammalian test systems (dominant lethal test and testicular DNA biosynthesis inhibition test). Possible prevention of mutagenic effects of INH using INH antitoxicants was also studied. INH without rat liver S9 mixture was mutagenic towards TA 100 and TA 1535. INH was not mutagenic to TA 92 or TA 98. Use of para-amino salicylic acid with INH significantly increased the number of revertants obtained. Two INH hydrazine metabolites, hydrazine sulfate (HS) and monoacetyl hydrazine (MAH), were mutagenic, HS for strains TA 92, TA 100, and TA 1535, and MAH for TA 100 and TA 1535. Negative results were obtained with diacetyl hydrazine and acetyl isoniazid. Of the three chemicals found to be positive, HS showed max mutagenicity in the presence of S9. Folic acid and pyridoxine slightly inhibited INH mutagenicity. The response of INH and HS was negative in the dominant lethal test. DNA synthesis in mouse testis was inhibited by INH, HS, MAH, and acetyl INH. It was concluded that the Ames test and the testicular DNA synthesis inhibition test show a good correlation in displaying mutagenicity of INH, HS, and MAH. (21 Refs)

29. ASSESSMENT OF MUTAGENIC POTENTIAL OF MIXTURES OF ORGANIC SUBSTANCES IN RENOVATED WATER.

Neal MW, Mason L, Schwartz DJ, Saxena J

Syracuse Univ. Res. Corp., New York, NY

Assessment of Mutagenic Potential of Mixtures of Organic Substances in Renovated Water. Available from National Technical Information Service, Springfield, VA, as PB81-153843:, 112 pp., 1981.

An investigation was undertaken to evaluate the performance of several advanced wastewater treatment plants having biological, physical chemical, or soils treatment systems for removing or introducing mutagenic substances. Samples were taken before and after treatment and sometimes at intermediate points. Both concentrated and unconcentrated wastewaters were used. Three different concentration methods were utilized and compared. Salmonella typhimurium, Saccharomyces cerevisiae, and mammalian cells were used in the test systems. Mutagenic activity was found to pass through most treatment plants and sometimes increased during treatment. Wastewater with no industrial wastes and strictly of domestic origin did not contain mutagenic properties. (Author abstract)

REVIEWS AND OTHER RELATED STUDIES

30. SHORT-TERM TESTS IN ASSESSMENT OF CANCER RISKS AND IN PRIMARY PREVENTION OF OCCUPATIONAL CANCER.

Schramm T

Bereich Chemische Kanzerogenese, Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany

Arch Geschwulstforsch; 52(1):75-81 1982

The use of short-term assays for carcinogenicity is reviewed. Short-term assays measure interactions at the cellular level, rather than measuring in vivo tumor-formation. Use of test batteries minimizes false positive and false negative results. Conclusive demonstration of carcinogenicity requires tumor induction in vivo. (47 Refs)

31. THE ROLE OF CYTOGENETIC TESTS IN DETECTION AND PREVENTION OF CANCER.

Bishun NP
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England
J Surg Oncol; 18(3):287-304 1981

Although simplified and improved techniques have increased at a fast rate in recent yr, a great number of compounds released into our environment still remain untested. It has been estimated that between 80-90% of human cancer is a result of exposure to such compounds, and if by the application of short-term mutagenic tests, the use of many of these compounds can be severely restricted, an enormous impact can be made on the solution of human health problems. Batteries of mutagenic tests have established an empirical relationship between mutagenesis and carcinogenesis, and, in view of the cost in terms of time and money, short-term tests are playing an important role in first detecting, and second, eliminating potential hazards in our environment. The use of bacteria and other unicellular organisms in these assay systems has met with much criticism; due to the fact that the DNA materials affected do not directly relate to that of man. However, in conjunction with other tests, utilizing human and other mammalian cells, firm conclusions can be drawn regarding the potential hazards of certain chemicals. Recent advances in cytogenetic tests (eg, banding chromosomes and sister chromatid exchange) have improved the sensitivity of chromosomal tests and, in so doing, have rendered them more useful in the selecting out process that can reduce substantially the mutagenic and carcinogenic hazards caused by chemicals and other deleterious agents in the environment. (Author abstract) (45 Refs)

32. A EUROPEAN COLLABORATIVE STUDY OF THE AMES ASSAY: I. RESULTS AND GENERAL INTERPRETATION.

Grafe A, Mattern IE, Green M
Boehringer Mannheim GmbH, Sandhofer Strasse 116, D-6800 Mannheim 31, W. Germany
Mutat Res; 85(6):391-410 1981

The Ames assay was performed for three test compounds (benzo(a)pyrene, N-nitrosomorpholine, and 2-aminoanthracene) in a collaborative study in 19 laboratories. Marked variations between test results occurred between and within laboratories; variability resulted partially from different interpretations of the guidelines, which allowed some flexibility. Results were also affected by other factors. Some variation was due to the level and quality of S9 preparations; different batches of S9 prepared in the same laboratory by a standard procedure may vary significantly in their properties. Other factors involve the number of cells used, differences in culture conditions, type and amount of solvent, number of plates used per concentration, and method of counting colonies. When results from all experiments were considered together, 60-80% were found within the half- to two-fold range of the overall median. Such a range might be considered satisfactory for a study not using rigidly standardized test conditions. Several recommendations for design and performance of future collaborative studies are given. (13 Refs)

33. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.

Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

Effects of chlorine residuals and organic compounds in drinking water and aquatic environments, particularly direct toxicity and/or carcinogenicity to human and aquatic life, are reviewed. Significant correlations between surface water chlorination and cancer mortality rates have been shown in humans. Elevated rates of bladder, rectal, colon, and gastrointestinal cancers in humans served by chlorinated water from the Mississippi River have been demonstrated. The use of chlorinated surface waters in Ohio was associated with stomach cancer in males and females, and with bladder cancer in males. Chloramine has been shown to be an extremely weak mutagen; involvement of DNA is suggested, since DNA-repair mutants are sensitive to the agent. In uremic patients, shortened RBC survival and hemolysis have been attributed to chlorinated tap water used in hemodialysis. Effects on aquatic life of chlorine residuals are reviewed. While more than 300 chlorinated organic compounds have been identified in chlorinated potable waters, cooling waters, and sanitary effluents, relatively little is known about their ecological effects. Laboratory research using animal models should focus on the chloramines and their effects on health. (65 Refs)

34. FLAVONOIDS, MUTAGENS, AND CITRUS.

Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

Data on the mutagenicity of flavonoids are reviewed. Of all classes of flavonoids, mutagenicity has been demonstrated only for some of the flavonols. Quercetin had the highest mutagenic activity in the Ames test in Salmonella typhimurium. The validity of the Ames test, however, depends on the activating agents used. Flavonols occur in almost all higher plant tissues and are common in human diets. The most common flavonols are quercetin and kaempferol, which almost always occur in the form of glycosides, which are nonmutagenic. Metabolism of quercetin glycosides is probably carried out along several pathways by intestinal microflora. Any occurrence of mutagenic quercetin aglycone is probably fleeting at most. Animal feeding studies of quercetin carcinogenicity have produced contradictory results. No evidence of absorption of free quercetin by the human gut has been found. Citrus fruits contain a wide variety of flavonoids. Any mutagenic activity of flavonols is probably affected by the presence of other flavonoids. Flavonol apparently present minimal risk in human diets. (46 Refs)

35. THE DECISION-POINT APPROACH FOR SYSTEMATIC CARCINOGEN TESTING.

Weisburger JH, Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):561-566 1981

The decision-point approach provides a framework, based on current concepts of the mechanisms of carcinogenesis, for systematic evaluation of potential mutagenic and carcinogenic hazards of chemicals. Chemical carcinogens have been divided into two main categories-genotoxic agents, which interact with DNA and genetic material and lead to irreversible alterations in DNA, and epigenetic agents, which operate by distinct nongenotoxic mechanisms and are tissue-specific. Genotoxic agents include direct-acting carcinogens, procarcinogens, and inorganic carcinogens; the first two classes damage DNA either through direct chemical reactivity or following metabolism by enzyme systems, whereas inorganic carcinogens are not directly genotoxic but lead to changes in DNA by selective alteration in the fidelity of DNA replication. Epigenetic agents include solid-stage carcinogens, hormones, immunosuppressors, co-carcinogens, and promoters. The decision-point approach involves five steps: (1) consideration of the structure of the chemical; (2) in vitro short-term tests (mutagenesis, DNA repair, chromosome effects, and cell transformation); (3) limited in vivo bioassays (skin-tumor induction in mice, pulmonary-tumor induction in mice, breast-cancer induction in rats, induction of rodent liver altered foci, and assays for promoters); (4) chronic bioassay; and (5) final classification of a chemical as a genotoxic or epigenetic carcinogen. Health-risk analysis also must consider quantitative potential as well as qualitative positive or negative results. The proposed testing approach provides for systematic yet economical testing, the results of which can be applied to flexible, rational health-risk analysis. (26 Refs)

36. INHIBITION OF VIRUS TRANSFORMATION BY HIGH ENERGY FUELS AS A CORRELATE OF CARCINOGENIC POTENTIAL.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Sci Tech Aerosp Rep; 19(18):2533 1981

Hydrazine and naphthylamines and their derivatives were assayed for co-carcinogenic effects on ST FeSV-directed transformation of human cells. All chemicals tested at non-toxic concentrations showed anti-carcinogenic activity. The temporal relationship of chemical treatment to virus infection was more critical with the hydrazines than with the naphthylamines in that max anti-carcinogenic effect occurred when virus-infected cells were exposed to the hydrazines 2 hr post-infection, whereas the naphthylamines anti-carcinogenic effect was observed if cells were exposed either pre- or post-infection. The anti-carcinogenic effect, when compared with in vitro chemical transformation and neoplastic transformation, show a high degree of correlation. These data suggest this assay system may lend itself to a rapid screen (9-13 days) of chemicals for carcinogenic potential. Cytotoxic results showed no significant difference in shale oil or petroleum derived JP5 or DFM. (Author abstract) (no Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.
Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
In GER

7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIO-PATHOGENESIS OF ACUTE LEUKAEMIA.
Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
Sangre (Barc); 26(5B):700-717 1981
In SPA

10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
In DAN

11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

17. GENITAL CANCER AND VIRUSES.
Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

SERIES CK19 No. 82/05

MAY, 1982

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TESTS FOR CELL TRANSFORMATION

1. COMPARATIVE NEOPLASTIC TRANSFORMATION RESPONSES OF BALB/3T3 CELLS, SYRIAN HAMSTER EMBRYO CELLS, AND RAUSCHER MURINE LEUKEMIA VIRUS-INFECTED FISCHER 344 RAT EMBRYO CELLS TO CHEMICAL CARCINOGENS.

Dunkel VC, Pienta RJ, Sivak A, Traul KA
Bureau Foods, Food and Drug Admin., Public Health Service, 200 C St., S.W., Washington, DC, 20204
JNCI; 67(6):1303-1315 1981

This study provides a preliminary comparative evaluation of the responses to a series of 49 chemicals, in in vitro transforma-

HE 20. 3173/2:

tion assays, of Balb/3T3 cells, Syrian hamster embryo cells, and Fischer 344 rat embryo cells infected with Rauscher murine leukemia virus. The chemicals assayed included aromatic amines; polycyclic aromatic hydrocarbons; alkylating agents; nitrosamines, hydrazines, and related compounds; heterocyclic compounds; amides, ureas, and acylating agents; inorganic compounds; and hormones. In all three assays 37 of the chemicals were tested. The most uniform test responses were obtained with the polycyclic aromatic hydrocarbons and inorganic compounds. With the other groups of chemicals, more variation in response was observed. This study expands the base of information on the potential of these in vitro transformation systems, and the lack of responses with some of the chemicals underscores the need for incorporation of exogenous metabolic activating systems into these assay systems. (Author abstract) (20 Refs)

2. IMMUNOGENICITY OF GUINEA PIG CELLS TRANSFORMED IN CULTURE BY CHEMICAL CARCINOGENS.

Ohanian SH, McCabe RP, Evans CH
Lab. Immunobiology, Div. Cancer Biology and Diagnosis, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI, 67(6):1363-1368 1981

The immunogenicity of inbred strain 2/N guinea pig fibroblasts transformed to the malignant state in vitro by chemical carcinogens was evaluated with the use of a variety of in vivo and in vitro methods including delayed-type hypersensitivity skin and tumor transplantation tests and analysis of antibody production by immunofluorescence, complement fixation, and staphylococcal protein A binding tests. Neoplastic transformation was induced by direct treatment of cells in culture with benzo[a]pyrene, 3-methylcholanthrene, or N-methyl-N'-nitro-N-nitrosoguanidine (NMMG) or by the host-mediated method by which fetuses were exposed to diethylnitrosamine or MNNG in vivo prior to cell culture. Rabbits and syngeneic guinea pigs were inoculated with unirradiated and x-irradiated clonally derived cells. Delayed hypersensitivity skin reactions to immunizing or other cells were equivalent in immunized or control guinea pigs, and no protection to tumor outgrowth from a challenge inoculum of immunizing cells was observed. Antibody activity induced in the sera of immunized guinea pigs was cross-reactive and removed by absorption with nontumorigenic cells. Rabbit antisera after absorption with fetal guinea pig cells were nonreactive with the specific immunizing or other cultured cells. Chemical carcinogen-induced neoplastic transformation of guinea pig cells can, therefore, occur without formation of detectable, individually distinct cell surface tumor-specific neoantigens. (Author abstract) (22 Refs)

3. CELL SHAPE CHANGES IN TRANSFORMATION (MEETING ABSTRACT).

Heckman CA, Olson AC
Biology Division and Computer Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire, Memorial Sloan-Kettering Cancer Center; 1981

Oncogenic transformation in cultured cells is frequently accompanied by changes in cell shape. To study the cellular mechanisms mediating these changes, we have developed a method for quantifying shape in individual cells. The method combines anodic oxide interferometry and computerized image analysis. The advantages were that information on three-dimensional shape was obtained, and that the problem of figure extraction from digitized images was avoided. The raw data were collected by tracing the first order interference contour, and as many higher order contours as possible, as closed figures on a graphics tablet connected to a PDP 11/70 computer. The coordinates of points on each contour were analyzed by computer programs to obtain values for the perimeter, area and major axis, and for 33 normalized parameters relating to curvature, eccentricity, departure from elliptical shape, and to the size and number of invaginations and projections. Additional parameters described the relationships among contours. To test the efficacy of the parameters for detecting differences in cell shape 3 cell lines which could be distinguished readily by phase microscopic examination were studied. For samples of 50 cells from each line the highest levels of misclassification seen were 14% by hierarchichal cluster analysis and 4% by linear discriminant analysis. Further analysis of a single cell line, 1000W, which became tumorigenic during in vitro culture showed that significant changes in shape occurred concomitantly. Max likelihood estimation showed a linear change over the time when tumorigenicity was attained. The prevalence of shape changes in progressing cell lines is currently under investigation. (1 Ref)

4. INHIBITION OF VIRUS TRANSFORMATION BY HIGH ENERGY FUELS AS A CORRELATE OF CARCINOGENIC POTENTIAL.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Aerosp Med Biol; (224):173 1981

Hydrazine and napthylamines and their derivatives were assayed for co-carcinogenic effects on ST FeSV-directed transformation of human cells. All chemicals tested at non-toxic concentrations showed anti-carcinogenic activity. The temporal relationship of chemical treatment to virus infection was more critical with the hydrazines than with the naphthylamines in that maximum anti-carcinogenic effect occurred when virus-infected cells were exposed to the hydrazine 2 hr post-infection, whereas the naphthylamine anti-carcinogenic effect was observed if cells were exposed either pre- or post-infection. The anti-carcinogenic effect, when compared with in vitro chemical transformation and neoplastic transformation, show a high degree of correlation. These data suggest this assay system may lend itself to a rapid screen (9-13 days) of chemicals for carcinogenic potential. Cytotoxic results showed no significant difference in shale oil or petroleum derived JP5 or DFM. (Author abstract) (no Refs)

IN VIVO TESTS FOR MUTAGENICITY

5. TUMORIGENESIS OF DIESEL EXHAUST, GASOLINE EXHAUST, AND RELATED EMISSION EXTRACTS ON SENCAR MOUSE SKIN.

Nesnow S, Triplett LL, Slaga TJ
Health Effects Res. Lab., Environmental Protection Agency, Research Triangle Park, NC
Sci Tech Aerosp Rep; 19(21):2960 1981

The SENCAR mouse skin tumorigenesis bioassay for tumor initiation, a quantitative short term in vivo rodent carcinogenesis system which detects a variety of structurally diverse chemical carcinogens was examined. This bioassay system is utilized in evaluating complex environmental mixtures for tumorigenic potential. It provides dose responses with both substances and complex mixtures and is utilized for comparative potency analysis. The tumorigenicity of diesel exhaust particulate emissions was examined using SENCAR mouse skin. The tumorigenic potency of particulate emissions from diesel, gasoline, and related emission sources are compared and the tumorigenic potential of the materials is clearly indicated. (Author abstract) (no Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

6. IN VITRO EFFECT OF SOME MUTAGENS/ CARCINOGENS ON CULTURED FISH CELLS.

Kocan RM, Landolt ML, Bond J, Benditt EP
Dept. Pathology SM-30, Univ. Washington, Seattle, WA, 98195
Arch Environ Contam Toxicol; 10(6):663-671 1981

Mutagenicity and toxicity of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and benzo(a)pyrene (BP) were tested in cell line BF-2 derived from the bluegill sunfish (Lepomis macrochirus). Both MNNG and BP exposure resulted in production of ouabain-resistant mutant colonies. The mutation frequency after exposure to MNNG (direct mutagen) was greater than that after exposure to BP (promutagen). BP at 5 and 20 ug/ml produced dose-dependent decreases in cell number. Incubation of BF-2 cells with BP at greater than 5 ug/ml resulted in formation of intracellular crystals. (20 Refs)

7. EQUIVALENCY OF ENDOTHELIAL CELL GROWTH SUPPLEMENT TO IRRADIATED FEEDER CELLS IN CARCINOGEN-INDUCED MORPHOLOGIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS.

Evans CH, DiPaolo JA
Lab. Biology, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
JNCI; 68(1):127-131 1982

Endothelial cell growth supplement (ECGS), an extract of bovine neural tissue with growth-promoting properties for human endothelial and epithelial cells and for mouse BALB/c fibroblast-like cells, can be substituted for feeder cells in a quantitative 7-day Syrian hamster embryo cell colony in vitro model of carcinogenesis. Inclusion of 50 or 100 ug ECGS/ml medium throughout the 7-day growth period produced results equal to those obtained with feeder cells. The frequency and morphology of normal fibroblast colonies and carcinogen-induced morphologically transformed cell colony growth in the presence of ECGS were similar to those in the presence of feeder cells. A positive dose-response relationship in transformation by benzo[a]pyrene occurred. The frequency of transformed colonies following UV irradiation and treatment of the cells with the cocarcinogenic tumor promoter 12-O-tetradecanoylphorbol 13-acetate was greatly augmented, and lymphotoxin, a lymphokine with anticarcinogenic activity, reduced transformation. Thus ECGS can substitute for feeder cells in supporting in vitro transformation and eliminates a potential complex source of variability for studies where interaction(s) with feeder cells are a consideration. The mechanics of this model system was simplified, and its versatility for the study of physiologic, carcinogenic, and other pathophysiologic processes was broadened. (Author abstract) (19 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

8. TESTS FOR MUTAGENICITY IN SALMONELLA AND COVALENT BINDING TO DNA AND PROTEIN IN THE RAT OF THE RIOT CONTROL AGENT O-CHLOROBENZYLIDENE MALONONITRILE (CS).

von Daniken A, Friederich U, Lutz WK, Schlatter C
Inst. Toxicology, Swiss Federal Inst. Technology, CH-8603 Schwerzenbach, Switzerland
Arch Toxicol; 49(1):15-27 1981

The aim of this study was to determine whether o-chlorobenzylidene malononitrile (CS) exhibits any genotoxic activity towards Salmonella or mammalian DNA in vivo. CS was synthesized with a [14C]-label at the benzylic carbon atom. It was administered ip at a dose level of 13 mg/kg (1 mCi/kg) to young adult male rats. Liver and kidney DNA was isolated after 8, 25, and 75 hr. The radioactivity was at (liver, 8 and 75 hr) or below (all other samples) the limit of detection of 3 dpm. Therefore, a possible binding of CS to DNA is at least 10(5) times lower than that of the strong hepatocarcinogen aflatoxin B1, and 4,000x lower than that of vinyl chloride. In contrast to this lack of DNA binding, but in agreement with the chemical reactivity of CS, a binding to nuclear proteins could be detected with specific activities ranging between 50 and 121 dpm/mg for liver and between 3 and 41 dpm/mg for kidney. Protein binding could well be responsible for its pronounced cytotoxic effects. CS was also tested in the Ames Salmonella/microsome assay. Strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were used with or without pre-incubation. Only with strain TA 100 and only without pre-incubation, a doubling of the number of revertants was detectable at the highest dose levels used, 1,000 and 2,000 ug CS per plate. With pre-incubation of TA 100 with CS, a slight increase of the number of revertants was seen at 100 and 500 ug per plate, and a subsequent fall below con trol values at 1,000 ug. A check for the number of surviving bacteria revealed a strong bacteriotoxicity of the higher doses of CS so that the calculated mutation frequencies, ie, the number of revertants per number of surviving bacteria, increased with doses up to 500 ug. This toxicity could be counteracted in part by the addition of increasing amounts of rat liver microsomes. In the view of these results, and taking into account the rare and low exposure of man, it is concluded that CS will not create a risk for the induction of point mutations or of carcinogenic processes mediated by DNA binding. (Author abstract) (26 Refs)

9. EFFECT OF METHYL SUBSTITUTION ON MUTAGENICITY OF 2-AMINO-3-METHYLIMIDAZO[4,5-F]QUINOLINE, ISOLATED FROM BROILED SARDINE.

Nagao M, Wakabayashi K, Kasai H, Nishimura S, Sugimura T
Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan
Carcinogenesis; 2(11):1147-1149 1981

The compound 2-Amino-3-methylimidazo[4,5-f]quinoline [I] is a potent mutagen isolated from broiled sun-dried sardine. [I] and its seven derivatives, (2 isomers, 1 demethylated derivative and 4 methyl-substituted derivatives), were tested for mutagenicity on Salmonella typhimurium TA98 and TA100 in the presence of S9 mix. 2-Amino-1,4-dimethylimidazo[4,5-f]quinoline was the strongest mutagen of these 8 compounds on TA98, giving 159,000 revertants/nmol (750,000 revertants/ug). The demethylated derivative, 2-aminoimidazo[4,5-f]-quinoline, had very weak mutagenicity, inducing only 55 revertants/nmol (200 revertants/ug). Compounds having a methyl group at position N-1 or N-3 of 2-aminoimidazo[4,5-f]quinoline were strong mutagens. The 1,5-dimethyl-derivative was more mutagenic than the 3,5-dimethyl-derivative. Introduction of a methyl group at position 4 and position 5 enhanced and reduced the mutagenicity, respectively. All the compounds tested were more mutagenic to TA98 than to TA100, but their relative orders of mutagenicity with TA98 and TA100 were the same. (Author abstract) (22 Refs)

10. MUTAGENICITY OF AIRBORNE PARTICLES FROM A NONINDUSTRIAL TOWN.

Whong WZ, Stewart J, McCawley M, Major P, Merchant JA, Ong TM
Div. Respiratory Diseases, Natl. Inst. Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505
Environ Mutagen; 3(6):617-626 1981

The mutagenicity of air particles from a nonindustrial university town was examined. Air samples were collected during June-December, 1980. Dichloromethane extracts of all samples exhibited mutagenic activity in Salmonella typhimurium TA98, but secondary ethyl acetate/methanol extracts did not. No mutagenic activity was observed in extracts of blank filters. The number of revertants ranged from 34-355/mg particles and from 35-455/10 cubic meters of air. Mutagenic activity of samples collected in June a nd July did not require S-9 activation, while the mutagenicity of samples collected in October, November, and December was enhanced by S-9 activation. Dichloromethane extracts were also mutagenic using the arabinose-resistant assay system; such mutagenicity was dose-dependent and could be detected at a sensitivity of 1 cubic meter air/plate. Mutagenic activity in TA98 was found in acidic and polynuclear aromatic fractions but not in neutral or basic fractions. Samples of coal fly ash from a university power plant extracted with dichloromethane were mutagenic. (21 Refs)

11. MUTAGENICITY OF URINARY METABOLITES OF BENZIDINE AND BENZIDINE-BASED AZO DYES.

Tanaka K, Mii T, Marui S, Matsubara I, Igaki H
Toray Shiga Hosp., 2-7-35 Sonoyama, Otsu, 520, Japan
Int Arch Occup Environ Health; 49(2):177-185 1981

Mutagenicity of urinary metabolites of benzidine and benzidine-based azo dyes was studied. Mutagenicity of the urine extracts was tested in the Salmonella/mammalian-microsome assay. Results of the mutagenicity assay and gas chromatography analysis of the urine extracts suggested that the azo dyes may decompose and release benzidine. The urinary metabolites of benzidine were more mutagenic than benzidine itself. Azo dyes studied were Direct Deep Black EX and Congo Red, both containing a 4,4'-diazobiphenyl group. (23 Refs)

12. DETECTION OF MUTAGENS IN COMPLEX SAMPLES BY THE SALMONELLA ASSAY APPLIED DIRECTLY ON THIN-LAYER CHROMATOGRAPHY PLATES.

Bjorseth A, Eidsa G, Gether J, Landmark L, Moller M
Central Inst. Industrial Res., P.O. Box 350, Blindern, Oslo 3, Norway
Science; 215(4528):87-89 1982

A new technique is reported in which components in complex samples are separated on thin-layer chromatography plates and their mutagenic effect is registered directly on the plates by means of the Salmonella assay. The method is quick and simple and particularly useful for screening large numbers of environmental samples. Qualitative comparisons of mutagens in different samples can easily be made. Registered mutagens can be identified by the chemical analysis of extracts from duplicate plates. (Author abstract) (13 Refs)

13. EVALUATION OF FOUR CONCENTRATION/EXTRACTION PROCEDURES ON WATERS AND EFFLUENTS COLLECTED FOR USE WITH THE SALMONELLA TYPHIMURIUM SCREENING PROCEDURE FOR MUTAGENS.

Dutka BJ, Jova A, Brechin J
Microbiology Lab. Section, Analytical Methods Div., National Water Res. Inst., Canada Centre for Inland Waters, P.O. Box 5050, Burlington, Ontario L7R 4A6, Canada
Bull Environ Contam Toxicol; 27(6):758-764 1981

Four concentration/extraction procedures, solvent extraction, adsorption onto XAD resins, flash evaporation, and membrane filtration, are compared for their ability to concentrate and extract potential mutagens from river, lake, and effluent samples. In conjunction with the procedures, three var iations of the Salmonella typhimurium test are assessed. (4 Refs)

14. MUTAGENICITY OF MAILLARD BROWNING PRODUCTS OBTAINED FROM A STARCH-GLYCINE MODEL SYSTEM.

Wei CI, Kitamura K, Shibamoto T
Lab. Energy-Related Res., Univ. California, Davis, CA, 95616
Food Cosmet Toxicol; 19(6):749-751 1981

The mutagenicity of organic solvent extracts obtained from a starch-glycine browning system was investigated. Samples from starch alone showed no mutagenic activity in the Ames test, but methylene chloride extracts of the starch-glycine mixture were mutagenic in a dose-dependent fashion. (18 Refs)

15. MUTAGENICITY OF 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, 4-NITROSOAZOBENZENE, 4-NITROAZOBENZENE, AND THEIR RING METHOXYLATED DERIVATIVES ON SALMONELLA.

Hashimoto Y, Watanabe HK, Degawa M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):921-929 1981

The mutagenicity of 4-aminoazobenzene (AAB), N-hydroxy-4-aminoazobenzene, 4-nitroazobenzene, and their 2-, 3-, 4'-methoxyl and 2,5-dimethoxyl derivatives, and 2-methoxy-4-nitrosoazobenzene and 3-methoxy-4-nitrosoazobenzene were examined on Salmonella typhimurium TA98 and TA100. The activities of AAB dyes upon S-9 metabolic activation were related to their carcinogenic activities in the rat. The potent carcinogen 3-methoxy-4-aminoazobenzene was a potent mutagen for both tester strains. The moderate or weak carcinogens 4'-methoxy-4-aminoazobenzene and AAB were moderate or weak mutagens for one or both of the tester strains. The noncarcinogens 2-methoxy-4-aminoazobenzene and 2,5-dimethoxy-4-aminoazobenzene were non-mutagenic. In contrast to AAB dyes, N-hydroxy-4-aminoazobenzene dyes showed greater mutagenicity than the mother AAB dyes, without S-9 treatment. 4-Nitroazobenzene dyes and 4-nitrosoazobenzene dyes showed mutagenicity without S-9 treatment, and the activities were related to those of the corresponding N-hydroxy-AAB dyes. All 4-nitroazobenzene dyes were mutagenic in the presence of S-9, suggesting the production of mutagens other than N-hydroxy-AAB dyes by the S-9 treatment. The cytotoxicity of azo dyes to bacteria had no apparent relation to the mutagenic activity of the azo dyes. Incubation of 4-nitroazobenzene dyes with TA100 bacteria yielded N-hydroxy-AAB dyes. The synthesis and properties of new N-hydroxy-AAB dyes, 4-nitroazobenzene dyes and 4-nitrosoazobenzene dyes are described. (Author abstract) (27 Refs)

16. DISTRIBUTION OF MUTAGENS IN TAMA AND AYASE RIVER SEDIMENTS.

Hirayama K, Suzuki J, Suzuki S
Faculty of Pharmaceutical Sciences, Science Univ. Tokyo, Tokyo 162, Japan
Rikusui Gaku Zasshi; 42(2):82-88 1981

DNA attacking ability and the mutagenic activity of water extracts from sediments of Tama and Ayase river were measured. The recombination-asay method using recombinationless mutant of Bacillus subtilis detected DNA attacking ability in water sediments of the Tama mid- and downstream and of the Ayase midstream. Mutagenic activity was detected in water sediments in both Tama and Ayase mid- and downstream. The reversion assay for mutagenic activity was performed using the Salmonella typhimurium strain TA 98. The mutagenic activity of water sediments causing changes in the metabolism of rat liver indicates the presence of a precursor which induces mutagenicity in the enzymes. The presence of various types of substances attacking DNA, acidic, neutral, and amphoteric compounds, was confirmed using the assay for pH fractionation of water extracts from sediments. Gel filtration chromatography confirmed that the chemicals in the two rivers are of different types. Monitoring river valleys by measuring the DNA attacking ability and the mutagenic activity of river sediments is important since a part of mutagenic substances or their precursors are discharged into rivers and streams. (4 Refs)

17. CIGARETTE SMOKING MAY YIELD NITROARENES.

McCoy EC, Rosenkranz HS
Dept. Epidemiology/Community Health, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Cancer Lett; 15(1):9-13 1982

Mutagenicity of cigarette smoke concentrate was tested on Salmonella strains TA98NR, TA98, and TA98/1,8DNP6. Mutagenicity was reduced by approx 70% in the strain TA98 which contains nitroreductase, compared to the TA98NR strain deficient in the nitroreductase. The present findings indicate that cigarette smoke condensates can be nitrated to mutagenic substances, exhibiting the properties expected of nitroarenes. Nitroarenes also appear to be generated during the smoking of cigarettes enriched with nitrates. (23 Refs)

18. FORMATION OF NITROSO COMPOUNDS AND MUTAGENS FROM CINNARIZINE, ETHAMBUTOL, PIROMIDIC ACID, PYRIDINOL CARBAMATE AND TIARAMIDE BY DRUG/NITRITE INTERACTION.

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Cancer Lett; 15(1):53-59 1982

The formations of nitroso compounds and mutagens from 5 nitrogen-containing drugs (cinnarizine, ethambutol, piromidic acid, pyridinol carbamate, and tiaramide) by drug/nitrite interaction were studied. The drugs (50 millimole) were reacted with nitrite (500 millimole) at pH 3.0-3.4 and 37 C for 4 hr, and the reaction mixtures were assayed for nitroso compounds and mutagens. Ethambutol, cinnarizine, and pyridinol carbamate yielded a considerable amount of nitroso compounds. The concentrations of drugs and nitrite used in the experiments were much higher than those expected to be present in the stomach after ingestion of therapeutic dosages of the drugs. Drug-nitrite interactions were examined under conditions presumed to resemble those in the stomach after ingestion of the drug to determine the possible extent of nitrosation during medication. The concentration of each drug was based on the max dose for adults and the estimated volume of the stomach content after a normal meal. The reaction product of pyridinol carbamate and nitrite was mutagenic to Salmonella typhimurium TA100 in the absence of S-9 mix. The formation of nitroso compounds was observed for ethambutol. Significant mutagenicity was detected in the reaction product of pyridinol carbamate. (15 Refs)

19. A MICROSUSPENSION ADAPTATION OF THE BACILLUS SUBTILIS 'REC' ASSAY.

McCarroll NE, Keech BH, Piper CE

Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180

Environ Mutagen; 3(6):607-616 1981

Sixty-six high mw or poorly soluble compounds were tested for mutagenicity in the Bacillus subtilis 'rec' assay. Six of 13 mutagenic aromatic amines were detected as preferential inhibitors of B subtilis M45. Nine polycyclic aromatic hydrocarbons, including benzo(a)pyrene, 3-aminopyrene, 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene, which do not elicit a genotoxic effect in Escherichia coli, were found to have preferential inhibitory activity towards M45. Anthracene, phenanthrene, and pyrene were inert. Dimethylnitrosamine and diethylnitrosamine both diminished growth of M45, as did a variety of other nitrosamines and hydrazines. The noncarcinogenic antimetabolite 5-fluoro-2'-deoxyuridine was genotoxic to M45. Acetamide, ethyl carbamate, methyl carbamate, and thiourea were inactive against M45, confirming results obtained using E Coli MSA and other microbial systems. All mutagenic alkylating agents except Captan were genotoxic in M45. In contrast to results obtained in E coli, 4-nitrobiphenyl was active in the M45 system. The lack of response in E coli may result from cell wall impenetrability of the compound. The contribution of solvents to toxicity in the B subtilis and E coli MSA systems is discussed. (13 Refs)

20. THE GENETIC ACTIVITY OF DINITROPYRENES IN YEAST: UNUSUAL DOSE RESPONSE CURVES FOR INDUCED MITOTIC GENE CONVERSION.

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Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales

Carcinogenesis; 2(11):1201-1205 1981

The compound 1,6-dinitropyrene (1,6DNP) and 1,8-dinitropyrene (1,8DNP) were tested for their ability to induce mitotic gene conversion at the trp 5 and his 4 loci in the yeast Saccharomyces cerevisiae JD1. Both compounds were shown to be potent inducers of gene conversion in yeast, with 1,6DNP being somewhat more active than 1,8DNP. Unusual dose-response curves were obtained in that toxicity and genetic activity decreased at the higher concentrations examined. This reduction in genetic activity may reflect a decrease in the ability of yeast cells to convert the dinitropyrenes to their mutagenic forms when the concentration of the compounds exceeds a certain level. (Author abstract) (13 Refs)

21. THE SALMONELLA MUTAGENICITY ASSAY ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi A, Bertoncini A, Zadro M

Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy

Arzneim Forsch; 31(12):2140-2142 1981

The antibacterial and antifungal imidazole derivative alpha-(2,4-dichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested for mutagenicity in Salmonella typhimurium in the Ames test. No mutagenicity was detected in strains TA 1535, TA 1537, TA 1538, TA 98, or TA 100 with or without microsomal activation. (5 Refs)

22. MUTAGENICITY STUDIES ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi D, Bertoncini A, Zadro M

Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy

Arzneim Forsch; 31(12):2142-2144 1981

The mutagenicity of alpha-(2,4-didichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested in a forward mutational assay in Schizosaccharomyces pombe and a mitotic gene conversion assay in Saccharomyces cerevisiae. No mutagenicity was detected in either test. In vivo mammalian studies are in progress. (5 Refs)

23. ANTIMUTAGENIC ACTIVITY OF BROWNING REACTION PRODUCTS .

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Cancer Lett; 15(1):27-33 1982

Antimutagenic effect was tested by exposing Salmonella typhimurium strain TA1535 in suspension to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the presence of products of 2 non-enzymatic browning reactions. The browning reaction products were obtained by heating a lysine-fructose mixture at 121 C for 1 hr and by caramelizing D-sucrose at 180 C for 1.5 hr. Solutions of MNNG were prepared by dissolving the carcinogen directly in phosphate-buffered saline (PBS). The second tested carcinogen, aflatoxin B1 was dissolved directly into dimethyl sulfoxide (DMSO) and then diluted with PBS to a final DMSO concentration of 5%. S typhimurium strain TA98 was used for studies involving aflatoxin B1 and the browning reaction products were added to the precarcinogen and an S9 mixture. The toxic effect of aflatoxin B1 + S9 mixture was abolished in the presence of the browning reaction products. The inhibitory action of non-enzymatic browning product reactions was tested on the direct-acting carcinogen and mutagen MNNG. A dose-dependent reduction in the mutagenic activities of both carcinogens was noted in the presence of the caramelized sucrose products. The mutagenic activity of both carcinogens was significantly suppressed by the browning reaction products. (22 Refs)

CYTOGENETIC TESTS

24. CHANGES IN LYMPHOCYTE MICRONUCLEUS RATE AND IN AMOUNT OF HAEMOGLOBIN F IN PERIPHERAL BLOOD OF WORKERS WITH LONG-TERM EXPOSURE TO BENZENE.

Wang Z, Chen Z, Sun X, Jiang L, Dai T, Feng B, Xia Y

Affiliated Hosp. Prevention and Treatment of Occupation Diseases, Sichuan Medical Coll., Chengdu, People's Republic of China

Zhonghua Yufangyixue Zazhi; 15(3):151-152 1981

Effects of benzene on 80 workers (48 men, 32 women; 18-53 yr old) exposed to the compound for 0.5-10 yr (av 2.5 yr) were investigated with the aid of the lymphocyte micronucleus test and tests for fetal Hb (HBF) and Hb A2 (HBA2) in peripheral blood. The median micronucleus rate was higher in the benzene workers than in the unexposed controls, with 12.5% of the former exceeding normal values (3 per 1,000), compared with 1.1% for the control group. The av HBF value in the benzene workers was 1.58% (0.67-3.60%), compared with 1.14% (0.60-1.86%) in the controls; this difference was statistically significant. The av HBA2 values appeared lower in the benzene workers (1.770 +-0.455%) than in the controls (1.908 +-0.392%), but the difference was not statistically significant. The effects of benzene on lymphocyte micronucleocyte rate and on blood HBF were dose dependent. The possible mechanism of benzene toxicity was discussed. (4 Refs) (In CHI)

25. THE INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY K-REGION EPOXIDES AND SOME DIHYDRODIOLS DERIVED FROM BENZ[A]ANTHRACENE, DIBENZ[A,C]ANTHRACENE AND DIBENZ[A,H]ANTHRACENE.

Pal K

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Mutat Res; 84(2):389-398 1981

Benz[a]anthracene (BA), dibenz[a,c]anthracene (DB[a,c]A), dibenz[a,h]anthracene (DB[a,h]A), and some of their metabolites were studied for induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells. BA and 1,2; 5,6-; 8,9-; and 10,11-diols induced some SCE, but they were not as active as either benz[a]anthracene 5,6-oxide, which induced an approx 2-fold increase in SCE at 1 ug/ml, or trans-3,4-dihydro-3,4-dihydroyxbenz[a]anthracene. Despite the strong cytotoxicity of DB[a,c]A, it did not induce SCE. However, all DB[a,c]A metabolites tested (1,2-; 3,4-; and 10,11-dihydrodiols) induced SCE in a dose-dependent manner; trans-1,2-dihydro-1,2-dihydroxybenz[a,c]anthracene (4 ug/ml) induced a greater than 4-fold increase in SCE. DB[a,h]A was only weakly active. Trans-3,4-dihydro-3,4-dihydroxydibenz[a,h]anthracene was the most active DB[a,h]A metabolite, producing a greater than 3-fold increase in SCE at 2 ug/ml. Dibenz[a,h]anthracene 5,6-oxide actively induced SCE in a dose-dependent manner, whereas the 5,6-and 1,2-diols were almost inactive. K-region 5,6-epoxides derived from BA and DB[a,h]A were more active than the parent hydrocarbon in inducing SCE. Data suggest that when activated, the three polycyclic aromatic hydrocarbons studied can be metabolized to the ultimate carcinogen in CHO cells possessing some microsomal monooxygenase. (35 Refs)

26. ULTRASONIC INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES.

Haupt M, Martin AO, Simpson JL, Iqbal MA, Elias S, Dyer A, Sabbagha RE
(c/o Martin) Dept. Obstetrics and Gynecology, Northwestern Univ. Medical, Chicago, IL
Hum Genet; 59(3):221-226 1981

Sister chromatid exchange (SCE) frequencies were analyzed using 'real-time' ultrasound as an indicator of DNA damage induced in human lymphocytes. Studies showed consistent small effects of ultrasound on SCE frequencies. A range of exposure times and intensities was tested in a series of blind, randomized, in vitro experiments under spatial and sonographic conditions simulating exposure of a gravid abdomen and uterus. Minimizing the numbers and lengths of exposure per patient appears prudent. (30 Refs)

27. PATULIN, A FURTHER CLASTOGENIC MYCOTOXIN, IS NEGATIVE IN THE SCE ASSAY IN CHINESE HAMSTER V79-E CELLS IN VITRO.

Thust R, Kneist S, Mendel J
Inst. Pathology, Medical Acad. Erfurt, Nordhauser Strasse 74, 50 Erfurt, E. Germany
Mutat Res; 103(1):91-97 1982

Clastogenicity of patulin (PT) was studied in Chinese hamster V79-E cells. Experiments demonstrated PT was a direct-acting clastogenic agent. Clastogenic activity was abolished when S9 mix (9,000 x gravity liver supernatant) was added, even at the S9-free cytotoxic concentration of 10(-5) M. Clastogenic activity was detected only within a narrow range: 22% aberrant mitoses at 5 x 10(-6) M and 8% at 2.5 x 10(-6) M. The concentration 10(-5) M was toxic. In further studies with V79-E cells, clastogenic effect depended on amount of incubation fluid as well as on number of cells treated, ie it depended on the number of molecules available per target cell. Within a dose range permitting survival of cells, PT did not induce an increase in the rate of sister chromatid exchange (SCE). Experiments on aberration kinetics showed a max rate 24 hr after treatment; SCE staining revealed that most cells underwent two S phases during this period. PT clastogenicity may be caused by interaction with chromosomal proteins; DNA does not appear to be the virtual target of this mycotoxin. (25 Refs)

28. INDUCTION BY INORGANIC METAL SALTS OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN HUMAN AND SYRIAN HAMSTER CELL STRAINS.

Larramendy ML, Popescu NC, DiPaolo JA
Lab. Biology, NCI, Bethesda, MD, 20205
Environ Mutagen; 3(6):597-606 1981

The frequency of sister chromatid exchange (SCE) and chromosomal aberrations (CAb) induced by several inorganic salts previously tested for transformation in Syrian hamster cells (HE C) was examined. Nontoxic concentrations of inorganic metal salts (sodium arsenite, beryllium sulfate, and nickel sulfate) that caused transformation in HEC increased SCE and CAb in human lymphocytes and HEC. Induced SCE frequencies were similar in the two cell types; increases were dose-related. Compared to control values of 5-18 and 7-20 SCE/cell in human and HEC cells, respectively, metals induced an SCE range of 10-35/cell. Sodium arsenite was most effective in human purified lymphocyte cultures, elevating SCE frequencies from 11.30 +-0.60 to 19.2 +-0.84 and 20.60 +-1.32 at 0.1 and 0.25 ug/ml, respectively. Sodium arsenate, beryllium sulfate, and nickel sulfate similarly increased SCE frequency but at 100x higher concentrations. Sodium arsenite and sodium arsenate, but not sodium tungstate, increased SCE frequency in whole human blood cultures. All tested inorganic metals except sodium tungstate induced SCE in HEC to approx 8x control values. CAb induction paralleled SCE induction, with chromatid aberrations being most frequent. (48 Refs)

29. SPONTANEOUS AND BUSULPHAN-INDUCED SISTER-CHROMATID EXCHANGE (SCE) FREQUENCIES IN HAEMATOLOGICALLY NORMAL HUMAN BONE MARROW AND LYMPHOCYTES.

Honeycombe JR
Dept. Cytogenetics and Immunogenetics, Inst. Cancer Res., Fulham Road, London SW3 6JJ, England
Mutat Res; 84(2):399-407 1981

Sister chromatid exchange (SCE) frequencies were determined in untreated and busulfan (BUS)-exposed lymphocytes and in bone-marrow cells from 17 untreated, hematologically normal patients with primary breast carcinoma or melanoma. Spontaneous SCE frequencies were in the range 3.13-11.07/cell for bone-marrow cells and from 8.13-13.30/cell for lymphocytes. SCE values were consistently lower in bone-marrow cells than in lymphocytes in all but one patient. Inter-patient variability in spontaneous SCE distribution was significant for both bone-marrow cells and lymphocytes. No correlation was noted between bone-marrow and lymphocyte SCE distribution, indicating that SCE values for the two tissues could be a tissue-specific phenomenon. The SCE technique gave a good quantitative assay of BUS-induced chromosome damage: both lymphocytes and bone-marrow cells from 14 of the cancer patients exhibited similar increases in SCE frequencies following in vitro exposure to the same BUS concentrations. Lymphocytes were in stage G0 when the drug was added prior to culturing, whereas bone-marrow cells were dividing: BUS may bind to DNA equally well at different stages of the cell cycle. Similar gradients of regression lines were obtained for pooled SCE data from bone marrow samples exposed to 0-2.0 ug/ml BUS, for bone-marrow samples exposed to up to 5.0 ug/ml BUS, and for previous lymphocyte SCE data; the ability of BUS to induce SCE is apparently the same in both tissues. (22 Refs)

30. MAMMALIAN SPERMATOGENESIS AS A BIOLOGIC DOSIMETER FOR RADIATION.

Hacker U, Schumann J, Gohde W, Muller K
Abteilung fur Experimentelle Tumorforschung, Universitat Munster, D-4400 Munster, W. Germany
Acta Radiol Oncol Radiat Phys Biol; 20(4):279-282 1981

Mouse spermatogenesis was used as an in vivo test system obviously suitable as a biologic dosimeter. Ionizing irradiation induced changes in the frequency distribution of the cellular DNA content of whole testis preparations. These changes can be analyzed by flow cytometry. Such measurements deliver information on: (1) an increase of the coefficient of variation of the DNA histograms of some spermatogenic cells, (2) induction of diploid mature sperm, and (3) the dose-depending inactivation of the highly sensitive differentiated spermatogonia. In this model especially No 3 delivers quantitative information on the cytotoxic action of ionizing irradiation and chemical noxae as well, whereas Nos 1 and 2 may be used as qualitative criteria of mutagenic action of physical and chemical agents, No 2 obviously being more sensitive than No 1. (Author abstract) (17 Refs)

31. FLOW CYTOMETRIC MEASUREMENT OF NUCLEAR DNA CONTENT VARIATIONS AS A POTENTIAL IN VIVO MUTAGENICITY TEST.

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Cytometry; 2(3):189-191 1981

Bone marrow samples from male NMRI mice administered cyclophosphamide (ip, 0.56-0.7 ml of 0.075-0.6% soln in physiological saline) were assayed for cellular DNA content. Staining was accomplished by addition of 9 ml disodium hydrogen phosphate containing 5 uM 4,6-diamidino-2-phenylindole, and fluorescence was measured by pulse cytophotometer. The coefficient of variation in the G1 peak of flow histograms increased during the first few days (especially 2-4 days) after injection. Both the magnitude and duration of the effect were dose-dependent through a range of 0-120 mg/kg. Reproducibility of results was high. (6 Refs)

32. INVESTIGATION OF THE SISTER CHROMATID EXCHANGE (SCE) FREQUENCY IN ONE PATIENT WITH XERODERMA PIGMENTOSUM.

Went M, Szorenyi A, Polay A, Simon N

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Arch Dermatol Res; 271(4):407-409 1981

The sensitivity of xeroderma pigmentosum (XP) cells from one patient to chemical mutagens was studied as a potential cytogenetic test. When the phytohemagglutinin-stimulated XP lymphocytes were exposed to mitomycin C prior to their first division, an increased rate of sister chromatid exchange (SCE) was observed. The high rate of SCE is a measurement of the amount of non-excisible or non-excised damage and consequently shows the altered capability of cells to repair DNA damage by a variety of physical and ch emical factors. (14 Refs)

33. POISSON GOODNESS-OF-FIT TESTS FOR RADIATION-INDUCED CHROMOSOME ABERRATIONS.

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Int J Radiat Biol; 40(6):685-692 1981

Asymptotic and exact Poisson goodness-of-fit tests have been reviewed with regard to their applicability in analyzing distributional properties of data on chromosome aberrations. It has been demonstrated that for typical cytogenetic samples, ie when the av number of aberrations per cell is smaller than one, results of asymptotic tests, especially of the most commonly used u-test, differ greatly from results of corresponding exact tests. While the u-statistic can serve as a qualitative index to indicate a tendency towards under- or over-dispersion, exact tests should be used if the assumption of a Poisson distribution is crucial, eg in investigating induction mechanisms. If the main interest is to detect a difference between the mean and the variance of a sample it is furthermore important to realize that a much larger sample size is required to detect under-dispersion than it is to detect over-dispersion. (Author abstract) (20 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

34. UNSCHEDULED DNA SYNTHESIS INDUCED BY 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, AND THEIR DERIVATIVES IN PRIMARY CULTURES OF RAT AND MOUSE HEPATOCYTES.

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Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan

Gan; 72(6):930-936 1981

The ability of carcinogenic and non-carcinogenic aminoazo dyes to induce unscheduled DNA synthesis (UDS) in primary cultures of hepatocytes of three strains of rats and two strains of mice was examined by means of microautoradiography. Azo dyes tested were 4-aminoazobenzene (AAB) and four of its ring methoxyl (MeO) derivatives, their N-hydroxy (N-OH) derivatives, N-methyl-4-aminoazobenzene (MAB) and its N-benzoyloxy derivative, and N,N-dimethyl-4-aminoazobenzene (DAB). All carcinogenic aminoazo dyes (AAB, 3-MeO-AAB, 4'-MeO-AAB, MAB and DAB), but not the non-carcinogenic dyes (2-MeO-AAB and 2,5-diMeO-AAB), induced UDS in rat hepatocytes as well as mouse hepatocytes. N-Hydroxy derivatives of AAB and its 3-and 4'-MeO derivatives elicited higher levels of UDS than did the corresponding mother aminoazo dyes. N-OH-2,5-MeO-AAB was as inactive with rat hepatocytes as the mother dye. N-OH-2,5-diMeO-AAB, however, elicited a definite level of UDS, in contrast to the mother 2,5-diMeO-AAB. N-Benzoyloxy-MAB, a prototype compound of the ultimate carcinogenic metabolite of MAB, was as active as the mother MAB. N-OH-3-MeO-AAB induced UDS more rapidly than did 3-MeO-AAB. The UDS elicited by 3-MeO-AAB was found to end within a few hours after releasing the hepatocytes from the azo dye. (Author abstract) (33 Refs)

35. DNA-REPAIR SYNTHESIS IN ATAXIA TELANGIECTASIA LYMPHOBLASTOID CELLS.

Ford MD, Houldsworth J, Lavin MF

Dept. Biochemistry, Univ. Queensland, Brisbane, 4067, Australia

Mutat Res; 84(2):419-427 1981

DNA-repair synthesis was assayed in lymphoblastoid cells from ataxia telangiectasia (AT) patients and from control cells following exposure to gamma-radiation (10-40 kilorad). NaI isopycnic gradient analysis and 3H-thymidine incorporation into acid-precipitable DNA in the presence of hydroxyurea indicated that AT heterozygote, AT homozygote, and control cells had similar capacities for repair of radiation damage. Rate and extent of dose-dependent inhibition of DNA replication by gamma-radiation were similar in the three groups of cells. Lack of difference between control and AT cells in degree of DNA-synthesis inhibition at the radiation doses used is likely due to a pronounced effect on overall DNA synthesis. (34 Refs)

36. DIFFERENTIAL SUSCEPTIBILITY OF CANCER AND NORMAL DNA TEMPLATES ALLOWS THE DETECTION OF CARCINOGENS AND ANTI-CANCER DRUGS (ONCOTEST) (MEETING ABSTRACT).

Beljanski M, Le Goff L, Beljanski MS
Laboratoire de Pharmacodynamie, 92290 Chatenay-Malabry, France
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium, European Organization for Research on Treatment of Cancer; 1981

Based on the differential template activity exhibited by DNA isolated from cancerous and healthy human or animal tissues, the Oncotest is an accurate and rapid assay for the screening of carcinogenic compounds. Thus, in the presence of all necessary components for radioactive DNA synthesis by DNA polymerase, carcinogenic compounds, antimitotic drugs (and miscellaneous compounds), at given concentrations strongly stimulate the synthesis of DNA isolated from different cancer tissues, but only slightly enhance that DNA from healthy tissues. Those carcinogens which cannot be characterized as mutagens in the Salmonella assay system, behave as carcinogens in the Oncotest. Carcinogenic potential of steroids can be shown by using the DNA from steroid hormone target tissue. There exists a common molecular mechanism through which carcinogens stimulate cancer DNA in vitro synthesis. Cancer DNAs are destabilized and in the presence of carcinogenic substances there is further DNA strand separation which accounts for the enhanced DNA synthesis. A correlation between in vitro cancer DNA synthesis, DNA strand separation and in vivo multiplication of cancerous cells can be demonstrated. Our assay system allows detection of those substances which selectively inhibit cancer DNA synthesis without affecting, in an appreciable way, that of DNA from healthy tissues. (no Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

37. ENHANCEMENT OF S9 ACTIVATION BY S105 CYTOSOLIC FRACTION.

Forster R, Green MH, Priestley A
Water Res. Center, Henley Road, Medmenham, Marlow, Buckinghamshire, England
Carcinogenesis; 2(11):1081-1085 1981

The addition of supplementary cytosolic fraction greatly enhances the activation of 2-acetylaminofluorene (AAF) by uninduced 9,000 x g supernatant fraction (S9) in the Ames test. Uninduced S9 is poor at activating AAF in the Ames test (although it is effective in the liquid based fluctuation test) probably because cytosolic material diffuses into the bottom agar. An enhancing effect of cytosol supplementation was also observed with 2-aminoanthracene (AA) and 2-aminofluorene (AF) with uninduced S9. Using Aroclor-induced preparations, supplementation with cytosol enhanced the activation of benzo[a]pyrene and ethidium bromide. With AAF and Aroclor-induced preparations, supplementation with cytosol produces a slight but significant increase in activation, but interpretation is complicated by the fact that Aroclor 105,000 x g supernatant fraction (S105) alone efficiently activates AAF, AF and AA. Norharman potentiated the enhancing effect of Aroclor S105 on Aroclor-S9 activation of AAF but inhibited the activation of AAF by S105 fraction alone. The enhancing effect of S105 fraction may explain some, but not all, of the differences between liquid-based and agar overlay based activation. (Author abstract) (26 Refs)

COMPARATIVE TEST RESULTS

38. INDUCTION OF SISTER CHROMATID EXCHANGES AND BACTERIAL REVERTANTS BY ORGANIC EXTRACTS OF AIRBORNE PARTICLES.

Lockard JM, Viau CJ, Lee-Stephens C, Caldwell JC, Wojciechowski JP, Enoch HG, Sabharwal PS
Graduate Center for Toxicology, Univ. Kentucky, 212 Medical Annex 5, Lexington, KY, 40506
Environ Mutagen; 3(6):671-681 1981

The genotoxicity of organic extracts of airborne particles collected in Lexington, Kentucky was evaluated. In sister chromatid exchange (SCE) assays conducted in human lymphocytes, extracts of all samples induced dose-related increases in number of SCEs. Concentrations of 60 or 80 ug extract/ml caused approximate doubling of background frequency of SCE, to 7.0-9.6 SCE/cell. No metabolic activation was used, indicating that compounds contained in the samples were either direct acting or activated by the lymphocytes. Addition of S9 activation induced negligible increases in number of SCEs for all samples in V79 Chinese hamster fibroblasts. Concentrations of more than 60-80 ug of the extracts were toxic to both human lymphocytes and V79 cells, inhibiting cell division and causing cell lysis. Dose related increases in number of bacterial revertants were induced by all of the organic extracts tested in the Ames assay with both TA98 and TA100. Addition of S9 caused no significant differences in reversion frequencies. (41 R efs)

REVIEWS AND OTHER RELATED STUDIES

39. TYPES OF MATERIALS AND TESTS (MEETING ABSTRACT).

Bridges JW, Hubbard SA
Robens Institute of Industrial and Environmental Health and Safety, University of Surrey Guildford, GU2 5XH, England
Mutagenicity Testing, October 12, 1981, London, England, Royal Society of Chemistry; 1981

Many carcinogens exert their effects indirectly through the formation of reactive metabolites. The formation of these reactive metabolites is brought about by the drug metabolizing enzymes of the cell, a group of enzymes whose primary role appears to be the conversion of lipid soluble substances to water soluble excretable products. In many mutagenicity tests a 9,000 xg fraction of rat liver homogenate (S9) is added to mimic the in vivo ability of tissues to form these reactive metabolites. The quantity and quality of S9 fraction which is added may cause large variations in the observed mutagenic response. The degree of mutagenicity is also affected greatly by the previous chemical exposure and diet of the rats from which the S9 fraction is derived. A number of other factors are also very important: a) The form in which the chemical is presented to the biological system. Particular problems are often experienced in assessing the mutagenicity of insoluble particulates, intensely colored materials, volatile substances and compounds which bind avidly to plastic. b) The medium in which the metabolizing and mutagenic response systems are suspended and the nature of any cellular membranes between them. This influences the passage of any reactive metabolites formed into the response system. c) The nature of the response system itself. No single set of experimental conditions is ideal for assessing the mutagenicity of all chemicals, rather the experimental conditions should be selected bearing in mind the physical and chemical properties of the material which is being tested. (no Refs)

40. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.

Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

The potential of ethylene oxide (EtO) as an occupational carcinogen is discussed. Production, use, potential for occupational exposure, evidence of carcinogenicity in experimental animals, mutagenic and reproductive effects, epidemiologic evidence of cancer in humans, exposure standards, and guides are reviewed. Results in sub-mammalian test systems (Salmonella typhimurium, Escherichia coli, Neurospora crassa, Tradescantia paludosa, and Drosophila melanogaster) have indicated mutagenic properties of EtO. EtO has caused statistically significant increases in mononuclear cell leukemia in female Fisher 344 rats. Among male Fisher 344 rats, EtO induced peritoneal mesothelioma originating in the testicular meso thelium. Investigation of possible adverse effects (analysis of chromosomal aberrations in lymphocytes for all exposed workers and sperm analysis for the men) has shown higher incidence of aberration and sister chromatid exchange among workers exposed to EtO. Cases of peripheral neuropathy among exposed workers have been reported. The present standard (1-10 ppm as 8 hr time-weighted av) may need to be reexamined; its adoption preceded recognition of the carcinogenic potential of EtO and was intended only to protect against acute and nonmalignant chronic effects. (no Refs)

41. HEALTH AND SAFETY IMPLICATIONS OF ALTERNATIVE ENERGY TECHNOLOGIES. III FOSSIL ENERGY.

Walsh PJ, Etnier EL, Watson AP
Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Environ Manage; 5(6):483-494 1981

Potential human health and safety concerns associated with coal gasification and liquefaction, recovery of oil from shale and tar sands, and enhanced natural gas recovery are discussed. The primary health concern with coal conversion processes is the potential for exposure to carcinogens, mutagens, and teratogens such as polycyclic aromatic hydrocarbons. Studies have shown that oils with lower boiling points (less than 260 C) have little carcinogenic activity in mice. However carcinogenic activity increases as the temperature in the process streams increases. Median length of latent period preceding cancer induction in mice shows an inverse correlation to the boiling point of oil. Direct human evidence is incomplete. Preliminary research indicates that synthetic crudes are more carcinogenic than natural crudes. (54 Refs)

42. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.

Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

Assays of mutagenicity currently being implemented in mammalian cells are reviewed along with a brief description of the methodology, advantages, and disadvantages, and correlation with known in vivo activity. Mammalian cell transformation assays discussed are mass culture, clonal assays, focus assays and soft agar assays. Mammalian cell mutation assays in vitro utilize both cell strains and continuous cell lines. Both established in vitro systems and systems being developed are outlined, as are in vivo-in vitro systems. Parameters associated with in vitro cell transformation and selection of drug-resistant phenotypes for detection of mutation in mammalian cells are outlined. The close association between mutagenic and carcinogenic activity for a large number of chemical compounds has focused attention on interaction between chemical carcinogens and cellular DNA. Studies on DNA fragmentation and DNA repair (unscheduled DNA synthesis) are briefly discussed. (44 Refs)

43. SHORT-TERM TESTS FOR CARCINOGENS AND THEIR USES (MEETING ABSTRACT).

Garner RC
University of York, York Y01 5DD, England
Mutagenicity Testing, October 12, 1981, London, England, Royal Society of Chemistry; 1981

Carcinogens can be divided into 5 major groups: (1) ionizing radiations; (2) viruses; (3) physical agents such as asbestos; (4) inorganic metal salts; and (5) organic chemicals. Group 5 constitutes the main class of substances giving rise to cancer. There are some 30 known organic chemicals or mixtures which can cause cancer in men, whereas some 2000 chemicals produce cancer in animals. If, as is the case, all known human carcinogens with the exception of arsenic can produce cancer in animals, it is likely that the reverse may also be true, namely that most animal carcinogens could produce cancer in humans. To test all the substances for which we have no biological data in animals would be an economic burden which could not be justified unless there were grounds for suspecting that chemical to be a hazard. To partially circumvent the problem of animal testing, a number of short-term tests for carcinogens have been devised. All rely on the unifying concept that organic chemical carcinogens are reactive chemical species (electrophiles) or must be metabolized to such. Chemical carcinogens will react with DNA, whether this be in bacteria or in mammalian cells, to cause an alteration in coding properties. In bacteria these reactions lead to mutations; in mammalian cells they lead to mutation and cancer. (no Refs)

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Vet Hum Toxicol; 23(6):439-443 1981

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Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

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Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

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Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

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Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

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Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

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Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

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8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

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10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
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Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

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13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
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JUNE, 1982

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TESTS FOR CELL TRANSFORMATION

1. A COMPARISON OF THE RESPONSE OF BHK21 C13 CELLS TO 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE IN A CELL TRANSFORMATION TEST.

Dehnel JM, Daniel MR, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):223-226 1982

Baby hamster kidney 21 C13 cell anchorage-dependent growth, demonstrable as the formation of macroscopically visible colonies after seeding in soft agar, was used to determine

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the carcinogenic potentials of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) . Transformation frequency and modification of supplementary criteria (dose-response relationship and doubling of number of transformed colonies in treated cultures compared to controls) were used as criteria of positive response. 4HMB satisfied all criteria for a positive response both in the presence and absence of metabolic activation. BC showed some evidence of transforming ability. The response of cells to 4CMB was inconsistent. (7 Refs)

2. THE ACTIVITY OF 4CMB IN THE BHK CELL-TRANSFORMATION ASSAY.

Styles J, Penman S
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 100(1-4):227-228 1982

The baby hamster kidney (BHK) transformation assay was used to study carcinogenic potential of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 2-acetylaminofluorene (2AAF). A positive response was obtained with 4CMB and 2AAF but a negative result was observed with BC. The BHK assay demonstrated that 4CMB is a potent in vitro transforming agent in the absence of S9 mix. BC, a known carcinogen, was negative in the assay, suggesting that 4CMB and BC were tested in a system where the conditions of the test did not reflect those in vivo. (6 Refs)

3. MUTAGENICITY TESTING ON NON-SELECTIVELY CLONED CHINESE HAMSTER OVARY CELLS WITH THE PROTEIN-MAPPING METHOD.

Zeindl E, Sperling K, Klose J
Institute fur Humangenetik, Freie Universitat Berlin, Garystrasse 9, D-1000 Berlin 33, Germany
Mutat Res; 97(1):67-78 1982

Protein mapping by two-dimensional electrophoresis (2DE) was used to study the mutagenicity of methylnitrosourea (MNU: 100 ug/ml) on Chinese hamster ovary cells cloned in nonselective media. Protein patterns were compared with respect to qualitative and quantitative differences between corresponding protein spots. Among 26 protein patterns obtained from the group of test clones, two different new protein spots were found, one each in two different patterns. No such variants were found in patterns of untreated clones. Protein spots showing differences in staining intensity or occurring in more than one but not all patterns (quantitative variants) were found more often in the test group. On average the quantitative variability in patterns of treated cells was 100% greater than in the control group. The cellular concentration of single proteins is considered a possible sensitive parameter for mutagenicity testing. (24 Refs)

4. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

Wilson WW, Khoobyarian N
(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680
Chem Biol Interact; 38(2):253-259 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 6.2-60.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

IN VIVO TESTS FOR MUTAGENICITY

5. DROSOPHILA, SEX-LINKED RECESSIVE LETHAL TESTS WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

MacDonald D, Telford K
Inst. Animal Genetics, West Mains Road, Edinburgh EH9 3JN, Scotland
Mutat Res; 100(1-4):335-338 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was studied in male Drosophila melanogaster. Larva were exposed to 4CMB or BC by feeding. Adults were exposed to 4CMB by feeding or by intra-abdominal injection. Males were then mated with females, and offspring were examined for sex-linked recessive lethal mutations. Neither 4CMB nor BC showed any significant toxicity or mutagenicity when given in doses of 5-660 ug. (1 Ref)

6. GENETIC ACTIVITIES OF 4-CHLOROMETHYLBIPHENYL, THE 4-HYDROXY DERIVATIVE AND BENZYL CHLORIDE IN THE SOMA AND GERM LINE OF DROSOPHILA MELANOGASTER.

Fahmy MJ, Fahmy OG
Dept. Genetics, Inst. Cancer Res., Pollard Woods Res. Station, Chalfont St. Giles, Buckinghamshire HP8 4SP, England
Mutat Res; 100(1-4):339-344 1982

Induction of alterations in gene expression by 4-chloromethylbiphenyl (CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in the soma and germ line of Drosophila melanogaster. Late embryos and newly hatched larvae were exposed to the test compounds in concentrations up to 2 milliM (mM) until maturation. Somatic alterations were measured by determining alterations in expression of the unstable w+ locus in mature treated males. At 0.5-2.0 mM, 4CMB, 4HMB, and BC increased the frequency of red eye sectors resulting from repression or deletion of the zeste-regulatory proximal subunits of the w+ locus. 4CMB and 4HMB had approx the same activity, while BC had an activity approx twice that of the other two compounds. At 0.5-2.0 mM concentrations 4HMB and BC each increased the frequency of occurrence of white eye sectors resulting from deletions within the structure of the w+ locus by approx one orde r of magnitude relative to untreated controls. 4CMB did not affect the occurrence of white sectors. Red sectors had a mean size of 27 +-6 ommatidia, corresponding to an eye anlage size of approx 30 cells at the time of induction. White sectors had a mean size of 87 +-17 ommatidia, corresponding to an eye anlage size of 9 cells at the time of induction. These findings indicate that induction of red sector occurred at or after the time of genetic determination during eye differentiation. The test compounds are apparently weak mutagens in the order 4CMB less than or equal to 4HMB less than or equal to BC. (5 Refs)

7. THE ASSAY OF 4-CHLOROMETHYLBIPHENYL IN THE DOMINANT LETHAL ASSAY IN MICE.

Wickramaratne GA, Richards D, Kilmartin M, Keetch D
Central Toxicology Lab., ICI Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 100(1-4):351-352 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB) was studied in an assay of dominant lethal mutation in Swiss Albino Alderley Park mice. Male mice received 4CMB po for 5 days and were then mated. Examination of uterine contents of females showed an increased in the number of early deaths per pregnancy only when the positive control substance, ethyl methanesulfonate, was used. 4CMB did not produce positive results. (1 Ref)

8. THE MUTAGENIC ACTIVITY OF QUERCETIN AND KAEMPFEROL IN DROSOPHILA MELANOGASTER.

Watson WA
Dept. Genetics, Univ. Aberdeen, Aberdeen, Scotland
Mutat Res; 103(2):145-147 1982

The frequencies of recessive sex-linked lethals were used to measure the mutagenic activity in Drosophila of three concentrations of quercetin and three of kaempferol, administered in 5% glucose soln. Adult Oregon-K wild type males were fed the solutions for 18 hr, and the standard Muller-5 test was followed. With the exception of four broods at the lowest doses, significant increases in recessive lethal frequencies were found for both compounds. (7 Refs)

9. SENSITIVITY OF DROSOPHILA MELANOGASTER TO LOW CONCENTRATIONS OF GASEOUS MUTAGENS: III. DOSE-RATE EFFECTS.

Kale PG, Baum JW
Safety and Environmental Protection Div., Brookhaven Natl. Lab., Upton, NY, 11973
Environ Mutagen; 3(1):65-70 1981

Sex-linked recessive lethal mutations were induced in Drosophila melanogaster males by chronic and acute exposures to gaseous 1,2-dibromoethane (DBE) in the range of 2.3-31.0 ppm/hr. Acute treatments corresponding to each chronic treatment were made by increasing concentration approx 30x with concomittant decrease in exposure period. Canton-S and Basc strains of D melanogaster were used to detect the mutations. Germ cell targets sampled, in order of decreasing sensitivity, were spermatocytes, spermatids, and spermatozoa. Total number of chromosomes tested and mutations confirmed in each daily brood for acute exposure, including previous data from chronic exposure at each of four exposure levels (EL) are presented. Each type of germ cell was tested in the immature and mature stage. No consistent pattern of difference was observed between acute and chronic exposure for three of the four EL. At the highest EL (30-31 ppm/hr), a consistent difference was observed between chronic and acute EL. At the higher EL in all three germ cells stages, the acute exposure showed significant increase in mutation frequency over chronic exposure. The greater acute vs chronic mutation frequency for spermatozoa, a metabolically inactive cell stage, indicates that the exposure rate effect at high EL levels is due to systemic factors such as metabolic deactivation or elimination, rather than repair of permutational damage in the target cells. The significance of these findings in risk assessment for environmental pollutants is discussed. (9 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

10. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

Li AP, Royer RE
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P. O. Box 5890, Albuquerque, NM
Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP + MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP + B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

11. CYTOTOXIC AND MUTAGENIC EFFECTS AT THE HGPRT LOCUS OF 4CMB IN V79 CHINESE HAMSTER CELLS.

Fox M
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):235-238 1982

Cytotoxic and mutagenic effects of 4-chloromethylbiphenyl (4CMB) at the HGPRT locus were assayed in V79 Chinese hamster cells. The spontaneous mutant frequency was significantly higher when 8-azaguanine (AZ) was used for selection than when 6-thioguanine (TG) was used. When 4CMB-treated cells were plated with AZ, an absolute increase in numbers of AZ-resistant colonies was observed at each expression time when cells were exposed to 4CMB doses between 30 and 60 ug/ml. Further increase in dose to 70 ug/ml resulted in a marked fall in number of colonies recovered. Data obtained using TG for selection were more variable due to the lower numbers of colonies scored, and a reproducible increment in actual number of colonies was not obtained at all expression times. The pooled data indicated some increase in induced mutant frequencies after exposure to 4CMB concentrations of 30 ug/ml or higher. The data indicated a weak positive response irrespective of AZ or TG selection. A possible threshold on the dose-response curve for induced mutation could differentiate 4CMB from direct-acting alkylating agents and UV light. (2 Refs)

12. THE MODIFYING EFFECT OF HEXAVALENT CHROMATE ON THE MUTAGENIC ACTIVITY OF THIO-TEPA.

Paschin YV, Kozachenko VI
Lab. Environmental Mutagens, Inst. General Genetics Acad. Sciences, Moscow 117809, USSR
Mutat Res; 103(3-6):367-370 1982

Logarithmically-growing cultures of Chinese hamster V79 cells were exposed to different concentrations of potassium dichromate (PD) or triethylene thiophosphoramide (thio-TEPA) for 2 hr, washed, in sterile Hank's soln, and incubated for 96 hr before 8-azaguanine selection and plating. The mutagenic effects of PD (0.5 ug/ml) and thio-TEPA (2 ug/ml) were virtuallly identical mutant frequencies: (11.2 vs 11.4, x 10(-5)), with little effect on the viability of cells. The same compounds together yielded a mutation frequency of 9.6 x 10(-5), but plating efficiency was reduced form 86% (PD) or 95% (thio-TEPA) to 67%. Administration of PD for 2 hr followed by thio-TEPA for 2 hr resulted in a mutation frequency of 20.7 x 10(-5), and a plating efficiency of only 12%. Thio-TEPA seems to act as a protectant in the combined administration by reducing hexavalent CR to the trivalent, nonmutagenic form; serial administration of the two mutagens results in an additive effect. (6 Refs)

13. A SIMPLE AUTORADIOGRAPHIC METHOD FOR ANNEALING HGPRT-DEFICIENCY IN COLONIES OF MAMMALIAN CELLS.

Thacker J, Stretch A, Brown R
MRC Radiobiology Unit, Harwell, Didcot, Oxon OX11 ORD, England
Mutat Res; 103(3-6):371-378 1982

An autoradiographic method based on (14C)hypoxanthine incorporation is described for assessing hypoxanthine-guanine phosphoribosyl transferase (HGPRT) activity in 6-thioguanine (TG)-selected V79-4 hamster cells directly in petri dishes. Problems of scoring of small nonmutant colonies, TG dosage and optimal TG concentration, and mutant expression time for radiation-induced mutants are discussed. Ionization radiation seems to produce TG-resistant mutants which predominantly have zero HGPRT activity. Other uses of the autoradiographic assay include measurement of adenine phosphoribosyl transferase activity in colonies by (14C)adenine incorporation, rapid identification of isolates with both HGPRT-proficient and HGPRT-deficient cells, finding the proportion of mutants with partial HGPRT activity, and a possible nonselective mutation system. (16 Refs)

14. EFFECT OF BC, 4CMB AND 4HMB ON THE MUTATION OF V79 CELLS TO AZAGUANINE RESISTANCE.

Lee CG, Webber TD
Chemical Defence Establishment, Porton Down, Salisbury, Wilts., England
Mutat Res; 100(1-4):245-248 1982

Conversion of 8-azaguanine (AG)-sensitive V79 Chinese hamster cells to AG-resistant cells was used to assay the mutagenicity of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB). Cytotoxic and mutagenic results were positive for BC and 4CMB. Results for 4HMB were considered negative; cell response to 4HMB was erratic. (no Refs)

15. MUTAGENIC EVALUATION OF CARCINOGENS AND NON-CARCINOGENS IN THE L5178Y/TK ASSAY UTILIZING POSTMITOCHONDRIAL FRACTIONS (S9) FROM NORMAL RAT LIVER.

Amacher DE, Turner GN
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Mutat Res; 97(1):49-65 1982

The detection capabilities of the modified mouse lymphoma L5178Y TK+/- to TK-/- mutation assay were tested using 5% (vol/vol) S9 from rodents (usually Sprague-Dawley rat) which had not been treated with enzyme inducers. Most suspected carcinogens (7/10) caused a doubling of mutant frequency compared to solvent controls in a minimum of one experiment, at treatment levels permitting at least 61% cell survival; the exception was 4-nitrobiphenyl, which was considered mutagenic when two-sample loge t-test was done. Thioacetamide, a carcinogen, was negative for both the 5% noninduced S9 and the 10% Aroclor 1254-induced S9 tests. Dimethylcarbamyl chloride and glycidaldehyde were mutagenic in the absence of S9 but showed diminished activity in the presence of 10% S9. Styrene oxide was also mutagenic without S9. Noncarcinogens (6/8) were negative for mutagenicity in the present test; exceptions were chloracetic acid and p-aminophenol. (18 Refs)

16. MUTATION AT THE TK LOCUS OF MOUSE LYMPHOMA L5178Y CELLS BY 4CMB, 4HMB AND BC.

Ross CA, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):249-251 1982

Mutation at the thymidine kinase locus of mouse lymphoma L5178Y cells was used to assay mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4-HMB), and benzyl chloride (BC). In the presence of S9 mix none of the compounds produced increased mutation relative to controls. Without S9 mix only 4CBM had significant mutagenicity. (1 Ref)

17. STUDIES WITH 4-CHLOROMETHYLBIPHENYL IN P388 CELLS SELECTED IN 5-IODO-2'-DEOXYURIDINE.

Anderson D, Cross MF
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr. Macclesfield, Cheshire, England
Mutat Res; 100(1-4):257-261 1982

The mutagenicity of 4-chloromethylbiphenyl (4CMB) was tested in P388 mouse lymphoma cells grown in the presence of 5-iodo-2'-deoxyuridine. Methyl methanesulfonate and benzo[a]pyrene were used as positive controls. 4CMB was mutagenic with or without S9 mix. With S9 mix, toxicity was lower with 60-min exposure than with 30-min exposure. Reduced toxicity may have resulted from detoxification of 4CMB by the S9 mix. (6 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

18. USE OF THE IMPROVED ARABINOSE-RESISTANT ASSAY SYSTEM OF SALMONELLA TYPHIMURIUM FOR MUTAGENESIS TESTING.

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Environ Mutagen; 3(1):95-99 1981

Improvement of the arabinose mutagenesis test system of Salmonella typhimurium by introducing an R factor plasmid (pKM101) into the testers is presented. Sensitivity of the R-factor plasmid containing tester strain S-50 and that of strain SV-21 was determined with three promutagens (2-aminoanthracene [2-AA], aflatoxin B1 [Afl B1], and benzo(a)pyrene [BaP]), three direct-acting mutagens (2-methoxy-6-chloro-9-[3(ethyl-2 chloroethyl)aminopropylamino]acridine x 2HCl [ICR-170], 2-methoxy-6-chloro-9-[3(2 chloroethyl)aminopropylamino]acridine x 2HCl [ICR-191], and methyl methanesulfonate [MMS]), and one air-sample oil shale ash extract (OSAE). The plate incorporation test with or without metabolic activation was used as the assay system. A weak or moderate mutagenic response to Afl B1, OSAE, and 2-AA and no response to MMS and BaP was observed in strain SV-21. High mutagenic response to all mutagens was noted in SV-50. With the R factor-containing strain (SVC-50), the mutagenic activity of Afl B1 can be detected at a dose of 10 nanog/plate. No mutagenic response to ICR-191 and weak mutagenic response to ICR-170 were observed with both strains when the standard selective medium was used. With addition of 0.2 mg glucose/plate in the selective medium, a substantial increase in sensitivity of both strains to the mutagens was observed. ICR-170 and ICR-191 were less mutagenic in SV-50 than SV-21. Results showed that addition of R factor plasmid (pKM101) substantially increases the mutagenic sensitivity of the tester to most mutagens tested, and that with tester SV-50, a simple plate incorporation test can be used in the arabinose mutagenicity system. (10 Refs)

19. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

Suter W, Jaeger I
Preclinical Res. Dept. Toxicology Unit, Sandoz Ltd., Basle, Switzerland
Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escherichia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519, and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify inclusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

20. A CORRELATION BETWEEN MUTAGENIC AND CARCINOGENIC POTENCIES IN A DIVERSE GROUP OF N-NITROSAMINES: DETERMINATION OF MUTAGENIC ACTIVITIES OF WEAKLY MUTAGENIC N-NITROSAMINES.

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Carcinogenesis; 2(12):1339-1344 1981

The mutagenic activities of a diverse group of N-nitrosamines were measured in Salmonella typhimurium TA 100 under conditions designed to maximize metabolism of N-nitrosamines and enhance their mutagenic effects. These conditions were also chosen since some of the carcinogens were previously reported to be non-mutagenic or of questionable mutagenic activity and some only became mutagenic after the bacteria were exposed to a 'threshold dose' of metabolites. The mutagenic potencies spanned a range of 10(5)-fold and correlated well with semiquantitative carcinogenic potencies taken from the literature. This correlation appears to be the strongest yet reported for any particular class of compounds. In addition, the mutagenic activities of a number of carcinogens, previously reported to be non-mutagenic, were determined. Among the structural features necessary for high mutagenic activity in this group of compounds was a potential, unsubstituted methylating or ethylating group. Substitution of alkyl, hydroxyl methoxyl, and cyano moieties at the alpha or beta carbon of these groups reduced mutagenic activity. (Author abstract) (34 Refs)

21. EFFECTS OF ORTHO-METHYL SUBSTITUENTS ON THE MUTAGENICITY OF AMINOBIPHENYLS AND AMINONAPTHALENES.

El-Bayoumy K, LaVoie EJ, Tulley-Freiler L, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 90(4):345-354 1981

Mutagenic activity (MA) of five aminobiphenyls and five aminonaphthalenes was studied in Salmonella typhimurium strains TA100, TA1535, and TA1538 using the Ames assay. Metabolic activation was provided by S9 mix prepared from the livers of male Fischer-344 rats treated with Aroclor. MA was observed only in the presence of S9. Of the aminobiphenyls only 4-aminobiphenyl (4ABP) showed MA; 4ABP was active against TA1538 and TA100 but not against TA1535. 4-amino-3-methylbiphenyl (4A3M) showed greater MA than 4ABP against TA1538; 3-amino-4-methylbiphenyl (3A4M) and 3-aminobiphenyl (3ABP) showed no MA against TA 1538. 3A4M showed MA against TA100, while 3ABP did not. Results indicate that the presence of an ortho-methyl group enhances the MA of aminobiphenyls. Among the 2-aminonaphthalenes 2-amino-3-methylnaphthalene (2A3M) had the greatest MA against TA1538, followed by 2-amino-1-methylnaphthalene (2A1M) and 2-aminonaphthalene (2AN). 2AN had the greatest MA against TA1535. Neither 1-aminonaphthalene (1AN) nor 1-amino-2-methylnaphthalene had any MA against TA1538 or TA1535. 1AN showed weak MA against TA100. Results indicate that the presence of an ortho-methyl group inhibits base-pair MA and enhances frame-shift MA in aminonaphthalenes. (22 Refs)

22. SYNERGISTIC EFFECTS OF INDIVIDUAL POLYCYCLIC AROMATIC HYDROCARBONS ON THE MUTAGENICITY OF THEIR MIXTURES.

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Mutat Res; 90(4):399-409 1981

Enhancement and inhibition of mutagenic activity (MA) of benzo[a]pyrene (B[a]P) by polycyclic aromatic hydrocarbons (PAH) was studied in Salmonella typhimurium strain TA98. S9 mix prepared from livers of Sprague-Dawley rats treated with Aroclor was used for metabolic activation. In the Ames assay bacterial cultures were exposed to B[a]P (0.5-3.0 ug/plate) with or without various PAH (less than or equal to 2,000 nanomoles/plate). Results obtained with PAH of 2-5 rings showed that all PAH tested enhanced MA of B[a]P. Naphthacene and benzo[e]pyrene enhanced MA of B[a]P at low concentrations but inhibited MA at higher concentrations. Neither naphthalene nor anthracene inhibited MA of B[a]P. Result s indicate that the amount of PAH required for enhancement and inhibition effects decreases with increasing number of rings in the PAH structure. Several compounds with four rings, such as chrysene, pyrene, fluoranthene, and triphenylene, were exceptions to this rule. The effects of compounds with five or more rings were difficult to interpret because their own mutagenicity interfered with the synergistic effect on B[a]P mutagenicity, and inhibitory effects were evident in every case. Synergistic effects are apparently dependent on the spatial geometry rather than on specific properties of the PAH. PAH did not increase MA of benzo[a]pyrene-4,5-oxide, a direct-acting metabolite of B[a]P. Since B[a]P requires metabolic activation for MA, the result suggests that PAH exert synergistic effects at the level of enzymatic activation of B[a]P. (19 Refs)

23. THE SALMONELLA/MICROSOME ASSAY: SOME POSSIBLE CAUSES FOR INTERLABORATORY VARIATIONS.

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Mutat Res; 103(2):133-140 1982

The influences of various parameters of minimal medium on the number of spontaneous and induced revertants of Salmonella typhimurium strains TA98 and TA100 were determined. Effects of differences in amounts of histidine, sterilization of histidine and biotin, preparation of minimal medium, amount of medium per plate, and storage times per plate were compared, using sodium azide and 2-nitrofluorene as reference mutagens. Recommendations are given for standardization of the Ames test. (13 Refs)

24. MUTAGENICITY OF AMINOCARBAZOLES AND NITROCARBAZOLES.

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Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Mutat Res; 90(4):337-344 1981

Mutagenic activity (MA) of the C-substituted nitro and amino derivatives of carbazole was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. As a metabolic activation system, S9 preparations were obtained from rats treated with Aroclor. Bacterial cultures were exposed to nitrocarbazoles (1, 2, 5, 10, 25, 50, 100, or 200 ug/plate) or aminocarbazoles (5, 10, 25, 50, 100, or 200 ug/plate). In the absence of S9, 2-nitrocarbazole (2NC) and 3-nitrocarbazole (3NC) were mutagenic towards TA98 cultures, while 1-nitrocarbazole (1NC) and 4-nitrocarbazole (4NC) were not. 2NC had MA similar to that of 2-nitrofluorene. In the presence of S9 the MA of 2NC and 3NC was reduced, 4NC showed weak MA, and 1NC remained inactive towards T98. 1NC and 3NC showed no MA towards TA100 with or without S9. 4NC showed MA towards TA100 with or without S9. 2NC showed weak MA with S9. All aminocarbazoles showed greater MA with S9 than without S9. 1-Aminocarbazole was inactive towards both TA98 and TA100. MA of 2-aminocarbazole was greater than that of 2-aminofluorene (2AF) without S9 and less than that of 2AF with S9. 3-Aminocarbazole showed moderate MA towards TA98 with S9 but no MA towards TA100. 4-Aminocarbazole showed MA towards TA100 but only marginal MA towards TA98. Because none of the test compounds showed MA towards the exclusive base pair tester strain TA1535, specificity in base pair or frame shift mechanism of action between isomers could not be confirmed. (15 Refs)

25. THE MUTAGENICITY OF DINITROTOLUENES IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(4):373-383 1981

Mutagenic activity (MA) of the six isomers of dinitrotoluene individually and in a mixture was studied using three assays with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100, and TM677. Metabolic activation was provided by microsomal preparations (PMS) from F-344 rats treated with Aroclor. S typhimurium were exposed to 2,3-dinitrotoluene (2,3-DNT), 2,4-dinitrotoluene (2,4-DNT), 2,5-dinitrotoluene (2,5-DNT), or 3,4-dinitrotoluene (3,4-DNT) (all at 200 ug/plate), 2,6-dinitrotoluene (2,6-DNT: 1,000 ug/plate), 3,5-dinitrotoluene (3,5-DNT: 40 ug/plate) or technical grade 2,4-DNT (TG). TG contained 76.5% 2,4-DNT, 18.8% 2,6-DNT, and small amounts of the other isomers. All samples tested showed MA in the Ames Salmonella/microsome test. The presence of PMS generally reduced MA of test compounds. MA was greatest in strains sensitive to frame-shift mutagens. 3,5-DNT had the greatest MA in inducing reversions to histidine prototrophy in strains TA98 and TA1538, as well as in a quantitative reversion assay in TA98. All samples tested increased the 8-azaguanine-resistant fraction of TM677 in a forward mutation assay; 3,5-DNT did not exceed the other isomers in MA in this assay. (19 Refs)

26. MUTAGENICITY OF GAMMA-IRRADIATED OXYGENATED AND DEOXYGENATED SOLUTIONS OF 2-DEOXY-D-RIBOSE AND D-RIBOSE IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(4):385-397 1981

Mutagenic activity (MA) of soln of 2-deoxy-D-ribose (2DDR) and D-ribose (DR) irradiated under different conditions was studied in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was provided by S9 mix prepared from liver homogenates from Wistar rats treated with Aroclor. Test soln were irradiated with gamma-radiation (0.12-0.14 kilogray(kGy)/min; total dose 10 kGy). Before and during irradiation highly purified O_2, N_2, or N_2O was bubbled through the soln. H_2O_2 present in irradiated oxygenated soln showed MA in TA98 and TA1537. MA of H_2O_2 was eliminated in the presence of S9. Irradiated soln of 2DDR or DR were mutagenic in TA98 and TA100 but not in the other strains. In the absence of S9, N_2O-saturated soln of 2DDR showed greater MA than N_2-saturated soln, suggesting that the OH radical is involved in production of mutagenic products of radiolysis. Malonaldehyde (MDA) was not mutagenic at concentrations produced by irradiation. MA of individual products of radiolysis were not determined. MA of irradiated 2DDR soln in TA100 increased with the level of aldehydes other than MDA. MA of irradiated 2DDR soln was reduced in a temperature-dependent manner by heating of the soln, supporting the hypothesis that MA is caused by carbonyl or dicarbonyl compounds. Autoclaved, nonirradiated soln of 2DDR showed no MA in S typhimurium. (22 Refs)

27. UKEMS COLLABORATIVE GENOTOXICITY TRIAL. BACTERIAL MUTATION TESTS OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE: ANALYSIS OF DATA FROM 17 LABORATORIES.

Venitt S

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Mutat Res; 100(1-4):91-109 1982

Results of bacterial mutagenicity assays of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) obtained by 17 laboratories are summarized and analyzed. Plate test, spontaneous mutation in plate tests, and fluctuation test data are reported. 4HMB was uniformly negative in plate tests using several strains of Salmonella typhimurium and one strain of Escherichia coli. In 183/206 plate tests, 4CMB produced positive dose-response curves, with slopes ranging from 0.01 to 57.9 mutants/ug. 4CMB was a potent, broad-spectrum mutagen, inducing mutations at frameshift loci (hisD3052 in TA1538 and TA98, and hisC3076 in TA1537) and base-pair substitution loci (hisG46 in TA1535 and TA100, and trpE ochre in E coli WP2uvrA(pKM101)). The only strains giving positive plate test results with BC were S typhimurium TA100 and E coli WP2uvrA(p). BC appears to be a base-pair substitution mutagen which does not require the addition of S9 for expression of mutagenic activity. Results from various laboratories were similar for plate tests. Plate and fluctuation test results are compared. (12 Refs)

28. UKEMS TRIAL COMPOUNDS: IN VITRO BACTERIAL MUTAGENICITY.

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Mutat Res; 100(1-4):45-47 1982

Mutagenicities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) were determined in the Ames test using Salmonella typhimurium TA1535, TA1537, TA98 and TA100. 4CMB elicited dose-related mutagenic activity against all of the listed tester strains in the presence of S9 mix, but was active against only TA1538, TA98, and TA100 in the absence of the activation system. In one assay with TA100, BC produced isolated increases in the numbers of revertant colonies in the presence of S9. 4HMB showed no evidence of mutagenicity. (4 Refs)

29. MUTAGENIC ACTIVITY OF BC AND 4CMB IN THE SALMONELLA SPOT TEST.

Hyldig-Nielsen F, Hartley-Asp B

Microbiology Dept., H. Lundbeck and Co., Valby, DK-2500 Copenhagen, Denmark

Mutat Res; 100(1-4):17-19 1982

The Salmonella spot test was used to test the mutagenicity of benzylchloride (BC) and 4-chloromethylbiphenyl (4CMB). 4CMB exhibited mutagenic activity in TA1538, TA98, and TA100 whereas BC was only active in TA100. 4CMB was active in TA100 at a lower concentration than BC. Thus, 4CMB exhibited a higher mutagenic potential than BC in the Salmonella typhimurium spot test. (1 Ref)

30. BACTERIAL MUTAGENICITY TESTS ON 4-CHLOROMETHYLBIPHENYL AND 2 STRUCTURAL ANALOGUES.

Kirkland DJ, Smith KL, Parmar V

Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 ILG, England

Mutat Res; 100(1-4):21-25 1982

Mutagenic activity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzylchloride (BC) was assayed in five strains of Salmonella typhimurium and two strains of Eschérichia coli using the Ames plate-incorporation method for reversion to His+ in Salmonellae, and a modified method for reversion to Trp+ in E coli. 4CMB showed strong mutagenicity causing both frameshift and base-pair substitution mutations. BC was a weak base substitution mutagen. 4HMB showed neither base substitution nor frameshift mutagenic activity. (4 Refs)

31. 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB): REVERSE MUTATION TESTS WITH SALMONELLA TYPHIMURIUM.

Ladner A

Toxicology Dept., Fisons Ltd., Loughborough, Leicestershire, England

Mutat Res; 100(1-4):27-31 1982

In vitro mutagenic activities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4-HMB) were compared. 4CMB produced strong mutagenic responses in Salmonella typhimurium strains TA1538 and TA98. Positive but somewhat weaker responses were also obtained with the third frame-shift detector TA1537. Tests with the two base-pair substitution detector strains gave conflicting results. 4CMB was strongly mutagenic for strain TA100 while results with TA1535 were equivocal. Slight indications of positivity were obtained with strain TA100 for BC. No evidence of genetic activity was seen in any of the five tester strains for 4HMB. (6 Refs)

32. EVALUATION OF 4-HYDROXYMETHYLBIPHENYL (4HMB), 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) USING THE AMES SALMONELLA/MICROSOME INCORPORATION TEST FOR MUTAGENICITY.

Moore WB, Chatfield SN
Dept. Bacteriology, Wellcome Res. Lab., Langley Court, Beckenham, Kent BR3 3BS, England
Mutat Res; 100(1-4):35-38 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to effect point mutations at histidine loci in each of five specially constructed strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) were determined in vitro using the Ames Salmonella/microsome incorporation test. The results indicated that 4HMB is neither a direct nor pro-mutagen, 4CMB is a direct mutagen, and BC is a direct mutagen of low potency. (3 Refs)

33. 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB): AN EVALUATION OF THEIR MUTAGENIC POTENTIAL USING SALMONELLA TYPHIMURIUM.

Jones E, Richold M
Dept. Mutagenesis, Huntgindon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):49-54 1982

Of three compounds tested using the Ames Salmonella typhimurium mutagenicity assay, only 4-chloromethylbiphenyl (4CMB) produced a strong positive response. No substantial increases in revertant colonies were observed following treatment with either benzyl chloride (BC) or 4-hydroxymethylbiphenyl (4HMB). No substantial increases in revertant colonies were observed following treatment with urine from mice dosed with 4CMB, BC, or 4HMB. The results indicated that the mutagenicity of 4CMB is considerably reduced, if not removed, when in vivo mutagenicity tests are used. (5 Refs)

34. 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE: A COMPARISON OF MUTAGENIC POTENTIAL USING THE SALMONELLA REVERSE MUTATION ASSAY.

Trueman RW, Callander RD
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):55-59 1982

The Salmonella reverse mutation assay was used to determine the mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). 4CMB gave a positive response in all five Salmonella tester strains, both in the presence and absence of S9. 4HMB gave a negative response in the presence of S9 with all strains. BC failed to give a positive response in any of the five strains in the absence of S9 mix. (2 Refs)

35. THE MUTAGENIC ACTIVITY OF 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) IN THE BACTERIAL/MICROSOME ASSAY.

Brooks TM, Gonzalez LP
Sittingbourne Res. Centre, Shell Res. Ltd., Sittingbourne, Kent, ME9 8AG, England
Mutat Res; 100(1-4):61-64 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was studied in agar layer cultures of Salmonella typhimurium TA1535, TA1537, TA1538, TA98, and TA100, and Escherichia coli WP2 and WP2uvrA. The mutagenic activity of benzyl chloride (BC) was investigated in only Salmonella strains. As says were performed with or without S9 activation. The results indicated that 4CMB is a direct-acting bacterial mutagen that shows a greater response in strains TA1538 and TA98, and that this activity is reduced in the presence of the S9 fraction. BC is a bacterial mutagen in strain TA100 only and the mutagenic response is increased by S9 mix. (4 Refs)

36. MUTAGENIC STUDIES ON BENZYL CHLORIDE, 4-CHLOROMETHYLBIPHENYL AND 4-HYDROXYMETHYLBIPHENYL WITH SALMONELLA TYPHIMURIUM AS PART OF THE UKEMS TRIAL.

Watkins P, Rickard C
Pharmaceuticals Div., Imperial Chemical Industries Ltd., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):65-66 1982

Mutagenicities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) were determined in histidine-dependent strains (TA1535, TA1537, TA1538, TA98, and TA100) of Salmonella typhimurium using a plate incorporation assay and S9 mix. BC showed a positive mutagenic response only with TA100 and only in the presence of S9 mix. 4CMB gave positive results with strains TA100, TA1535, and TA1538, with or without S9 mix. With strains TA98 and TA1537, 4CMB only gave a positive response in the presence of S9 mix. 4HMB showed no positive results with any of the strains tested. (1 Ref)

37. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN THE SALMONELLA/MICROSOME ASSAY.

Pagano DA, Shelby MD
Natl. Inst. Environmental Health Sciences, Triangle Park, NC, 27709
Mutat Res; 100(1-4):67-70 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was determined in Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 using the plate incorporation assay with and without rat-liver S9. 4CMB was positive in strains TA1537, TA98, and TA100 both with and without S9 activation. A weakly positive response was seen with strain TA1535 tested without activation. (4 Refs)

38. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN REPAIR-DEFICIENT STRAINS OF SALMONELLA TYPHIMURIUM.

Forster R
Water Res. Centre, Henley Road, Medmenham, Marlow, Bucks SL7 2HD, England
Mutat Res; 100(1-4):75-79 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was examined in a series of repair deficient derivatives of Salmonella typhimurium LT2 using the fluctuation test. 4CMB was mutagenic to frameshift tester strains at 0.01-50 ug/ml, except in genetic backgrounds; no mutagenicity was observed in base-pair substitution tester strains at the dose levels used, except in the presence of the plasmid pKM101. Thus 4CMB appears to be primarily active as a frameshift mutagen. A much greater effect was seen in the excision-deficient strain TA1533 than in the repair wild-type strain D3052, suggesting that 4CMB forms an excisable DNA adduct. Increased cellular permeability resulting from the 'deep rough' (rfa) mutation led to greater mutation production by 4CMB, as can be seen by comparison of results for strains TA1533 and TA1538 which are isogenic except for the rfa mutation in TA1538. Strain TS27, which carries the recA allele and is completely deficient in recombination and error-prone repair, was almost as sensitive to 4CMB mutation as D3052; such a result suggests that a substantial proportion of the frameshift activity of 4CMB is independent of rec-lex function, consistent with the finding that the plasmid pKM101 has no observable effect on frameshift mutation by 4CMB and strains TA98 and TA1538 are equally sensitive to 4CMB mutation. The mechanism of 4CMB mutagenesis is discussed. (14 Refs)

39. AN ASSAY FOR MUTAGENIC ACTIVITY OF 4CMB, 4HMB AND BC, USING THE 'MICROTITRE' FLUCTUATION TEST.

Pour MS, Merrill C, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):81-85 1982

The 'microtiter' bacterial fluctuation test was used to examine mutagenicity of 4-chloromethylbiphenyl, 4-hydroxymethylbiphenyl, and benzyl chloride in Salmonella typhimurium strains TA 98 and TA100; the strains are sensitive to frameshift and base-substitution mutagens, respectively. Only 4CMB was found to be a potent base-substitution and frameshift mutagen. (3 Refs)

40. FLUCTUATION TEST DATA ON 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC) USING SALMONELLA TYPHIMURIUM TA98 AND TA100.

Sargent AW, Regnier AP
British Petroleum Res. Centre, British Petroleum Co. Ltd., Chertsey Road, Sunbury-on-Thames, Meddx. TW16 7LN, England
Mutat Res; 100(1-4):87-90 1982

Bacterial fluctuation tests were performed with and without metabolic activation using the Ames Salmonella typhimurium strains TA98 and TA100. The mutagenic potential of benzyl chloride, 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was assayed. 4CMB was mutagenic both with and without metabolic activation in TA100 and TA98. Data for 4HMB was negative. BC was non-mutagenic. (4 Refs)

41. IN VIVO AND IN VITRO STUDY OF MUTAGENICITY OF CARCINOGENIC N-NITRAMINES.

Khudolei VV, Malaveille C, Bartsch H
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(11):59-62 1981

The mutagenicity of dimethylnitramine, diethylnitramine and nitromorpholine was established in host-mediated assay with Salmonella typhimurium TA 1530 as indicator organism. It was demonstrated in experiments involving isolation of the bacteria from liver that enzymatic activation is required for bringing about the mutagenic effect of diethylnitramine. In in vitro experiments it was shown that carbonium cation is responsible for the carcinogenic and mutagenic effects of nitramines. (Author abstract) (11 Refs) (I n RUS)

42. THE MUTAGENIC POTENTIAL OF: 3-NITROPHENYL DIMETHYLPHOSPHINATE, 4-NITROPHENYL 4-METHOXYPHENYL (METHYL) PHOSPHINATE, 4-NITROPHENYL 4-METHYLPHENYL (METHYL) PHOSPHINATE, 4-NITROPHENYL DI-N-BUTYLPHOSPHINOTHIOATE.

Sauers LJ, Pulliam FR, Fruin JT

Letterman Army Inst. Res., San Francisco, CA

The Mutagenic Potential of: 3-Nitrophenyl Dimethylphosphinate, 4-Nitrophenyl 4-Methoxyphenyl (Methyl) Phosphinate, 4-Nitrophenyl 4-Methylphenyl (Methyl) Phosphinate, 4-Nitrophenyl di-n-butylphosphinothioate. Available from National Technical Information Service, Springfield, VA, as AD-A105 489/9:, 35 pp., 1981.

The mutagenic potential of 3 nitrophenyl dimethylphosphinate; 4-nitrophenyl 4-methoxyphenyl(methyl)phosphinate; 4-nitrophenyl(methyl)phosphinate; 4-nitrophenyl di-n-butylphosphinate was assessed by using the Ames Salmonella/Mammalian Microsome Mutagenicity Assay. Tester strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to doses ranging from 1 mg/plate to 3.2 x 10(-4) mg/plate. It was determined that none of the tested substances had mutagenic potential. (Author abstract)

43. THE MUTAGENIC POTENTIAL OF 4 NITROPHENYL BIS(2-THIENYL)-PHOSPHINATE; 4-NITROPHENYL 2-FURYL(METHYL)-PHOSPHINATES; 4-CYANOPHENYL BIS(2-FURYL)-PHOSPHINATE; 4-NITROPHENYL BIS(2-FURYL)-PHOSPHINATE.

Sauers LJ, Pulliam FR, Fruin JT

Letterman Army Inst. Res., San Francisco, CA

The Mutagenic Potential of 4 nitrophenyl bis(2-thienyl)-phosphinate; 4-nitrophenyl 2-furyl(methyl)-phosphinates; 4-cyanophenyl bis(2-furyl)-phosphinate; 4-nitrophenyl bis(2-furyl)-phosphinate. Available from National Technical Information Service, Springfield, VA, as ADA105 978/1:, 37 pp., 1981.

The mutagenic potential of 4 nitrophenyl bis(2-thienyl)phosphinate; 4-nitrophenyl 2-furyl(methyl)phosphinate 4 cyanophenyl bis(2-furyl)phosphinate; 4-nitrophenyl bis(2-furyl)phosphinate was assessed by using the Ames Salmonella/Mammalian Microsome Mutagenicity Assay. Tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to doses ranging from 1 mg/plate to 0.00032 mg/plate. It was determined that none of the tested substances had mutagenic potential. (Author abstract)

44. MUTAGENS IN DIESEL EXHAUST PARTICULATE: IDENTIFICATION AND DIRECT ACTIVITIES OF 6-NITROBENZO(A)PYRENE, 9-NITROANTHRACENE, 1-NITROPYRENE AND 5H-PHENANTHRO[(4,5-BCD)]PYRAN-5-ONE.

Pitts JN, Lokensgard DM, Harger W, Fisher TS, Mcjia V, Schuler JJ, Scorziell GM, Katzenstein YA

Statewide Air Pollution Res. Center, Univ. California, Riverside, CA, 92521

Mutat Res; 103(3-6):241-249 1982

Combined chemical/microbiological analyses of diesel exhaust particulate organic matter (POM) are reported. Levels of three nitroarenes 1-nitropyrene (1NP), 9-nitroanthracene (9NA), and 6-nitrobenzo(a)pyrene (6NBP) were determined. A new type of direct mutagen in combustion-generated POM, 5H-ph enanthro(4,5-bcd) pyran-5-one (IPAP) had been also determined. The base + neutral/(bn) fractions of dichloromethane (DCM) extracts of diesel exhaust POM were much more mutagenic than the acid fraction in the Ames test with Salmonella strains TA98 and TA98R, and the latter strain, a nitroreductase-deficient isolate of TA98, showed less response, indicating that direct activity of the bn fraction was due to nitrosubstituted compounds. The presence of 1NP, 9NA, 6NBP, and IPAP in the bn fraction was confirmed by capillary gas chromatography/mass spectra analysis and other tests. Highly purified samples of the four compounds were compared using the Ames test with the standard mutagens quercetin, 2-nitrofluorene and benzo(a)pyrene, and the other mutagens (1 or 3)-nitrobenzo(a)pyrene and (3 or 1)-nitrobenzo(a)pyrene. 1NP accounted for 20 and 27% of the direct mutagenic activity exhibited by the total DCM extract and bn fraction, respectively. The compound accounts for about 50% of the 'nitroarene' portion of the direct activity, defined here as the difference between TA98 and TA98R responses, whereas 9NA and 6NBP make negligible contributions to the total activity. The activity of the lactone IPAP is reported here for the first time, and UV, fluorescence, and mass spectra data for the compound are given. (47 Refs)

45. MUTAGENICITY OF PARTICULATES IN SMALL ENGINE EXHAUST.

Ohnishi Y, Okazaki H, Wakisaka K, Kinouchi T, Kikuchi T, Furuya K

Dept. Bacteriology, Sch. Medicine, Univ. Tokushima, Tokushima 770, Japan

Mutat Res; 103(3-6):251-256 1982

Mutagenic activities of particulates in filtered exhaust from a small gasoline engine, a small diesel engine, and the new NiCE (Nippon Clean Engine Research Institute) thermo-atmosphere combustion gasoline engine were compared using the Ames test (strains TA98 and TA100; with and without S9). Generally the number of revertants in colonies treated with NiCE engine exhaust extracts was much lower than colonies treated with exhaust extracts of either the traditional gasoline engine or the small diesel engine. With a catalytic muffler emissions from the NiCE engine were markedly less mutagenic; no benzo(a)pyrene emissions were detected by high performance liquid chromatography of the muffled exhaust. (13 Refs)

46. THE EFFECTS OF NITROUS ACID ON THE MUTAGENICITY OF TWO COAL LIQUIDS AND THEIR GENETICALLY ACTIVE CHEMICAL FRACTIONS.

Pelroy RA, Stewart DL

Pacific Northwest Lab., Richland, WA, 99352

Mutat Res; 90(4):297-308 1981

The mutagenicity of solvent refined coal (SRC) distillates and distillate fractions was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. Chemicals tested included SRC-II heavy distillate (HD), SRC-I process solvent (PS), basic tar and neutral tar fractions of HD and PS, and samples of these chemicals that had been treated with either HCl or HNO2. SRC samples dissolved in dimethylsulfoxide or emulsified in HCl medium contained mutagens that required activation by S9 enzymes. Treatment of SRC samples with HNO2 reduced the observed mutagenicity. Mutagens detected after HNO2 treatment were direct acting; mutagenicity of the substances was apparently decreased by S9 enzymes. HCl did not decrease the mutagenicity of SRC samples. In the absence of S9 enzymes, mutagenicity of SRC compounds was reduced by 73% for PS, 80% for PS basic and neutral tars, and at least 90% for other SRC samples, compared with untreated samples. In the presence of S9 enzymes all HNO2-treated samples showed less than 10% of the mutagenicity of untreated samples. HNO2 treatment did not reduce mutagenicity of the nonprimary aromatic amine polycyclic compounds phenanthridine, dimethylbenzacridine, benzo[a]pyrene, and 2-acetylaminofluorene. Results suggest that primary aromatic amines are the most important contributors to mutagenicity of SRC distillates in the Ames assay system. (21 Refs)

47. MUTAGENIC CHARACTERIZATION OF SYNTHETIC FUEL MATERIALS BY THE AMES/SALMONELLA ASSAY SYSTEM.

Pelroy RA, Petersen MR

Biology Dept., Pacific Northwest Lab., P.O. Box 999, Richland, WA, 99352

Mutat Res; 90(4):309-320 1981

Mutagenicity of solvent refined coal (SRC) distillates from two pilot processes (SRC-I and SRC-II) was studied in Salmonella typhimurium TA98. Samples tested included SRC-II heavy (HD), medium, and light distillates and SRC-I process solvent (PS), wash solvent, and light oil. HD and PS contained high-mol wt, high-boiling point compounds; of the crude samples only HD and PS showed mutagenic activity (MA). Dose-response curves were approx linear for HD and PS at 1-10 ug/plate. All MA required metabolic activation by S9 enzymes. Analysis of fractions of PS and HD obtained by solvent fractionation showed that specific MA was high for basic fractions, intermediate for basic tar and neutral tar fractions, and low for acidic tar fractions. Neutral, aliphatic, and neutral polyaromatic hydrocarbon-enriched fractions showed little or no MA. Fractions of PS obtained after solvent extraction accounted for 125% of the MA of crude PS; fractions of HD accounted for 88% of the MA of crude HD. Although the basic fractions of PS and HD had the highest specific MA, the basic tar and neutral tar fractions contributed the greatest portion of overall MA because these fractions made up 50% of the total weight of crude PS and HD compared with 1% of the basic fractions. The basic fractions of PS and HD had MA comparable to that of benzo[a]pyrene but less than that of 2-aminoanthracene. (25 Refs)

48. INVESTIGATION OF MAILLARD PRODUCTS IN BACTERIAL MUTAGENICITY TEST SYSTEMS.

Aeschbacher HU, Chappuis C, Manganel M, Aeschbach R
Res. Dept., Biological Experimentation Services Orbe, Nestle Products, Technical Assistance Co., Ltd., CH-1350 Orbe VD, Switzerland
Prog Food Nutr Sci; 5(1-6):279-293 1981

In view of the recent interest in possible cancer risk from heated foods, the Ames test for mutagenicity was performed on certain heated foods. The plate mutagenicity test using Salmonella tester strains TA 1535, 1537, 1538, 98 and 100 was employed with and without metabolic activation. Food caramel, obtained from heating pure sugar, was not mutagenic. A liquid preparation was tested as was a powder and its three fractions. A plant protein hydrolysate (Maggie seasoning) also was found to be nonmutagenic. A heated mixture of arginine-glucose induced a slight mutagenic effect in Salmonella TA 100 (base pair substitution) but not in TA 98. The effect was abolished when the microsomal fraction (S-9 mix) was present together with the arginine-glucose. The pure compounds 2,5 dimethyl pyrazine and hydroxy-methylfurfural were negative in the Ames test. (11 Refs)

49. SYNTHESIS, CHEMICAL CHARACTERIZATION, AND MUTAGENIC ACTIVITIES OF PROMUTAGENS PRODUCED BY PYROLYSIS OF PROTEINACEOUS SUBSTANCES.

Peters JH, Mortelmans KE, Reist EJ, Sigman CC, Spanggord RJ, Thomas DW
Life Sciences Div., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Environ Mutagen; 3(6):639-649 1981

Synthetic, structural and biological properties of TRP-P-1 (tryptophan pyrolysis product), TRP-P-2, GLU-P-1 (glutamic acid pyrolysis product), GLU-P-2, GLOB-P-1 (2-amino-3-methyl-9H-pyrido(2,3-b)-indole), and GLOB-P-2 (2-amino-9H-pyrido(2,3-b)-indole) were examined. While these compounds proved to be 99% pure, impurities associated with TRP-P-1 and J-TRP-P-1 included a side product of the final cyclization step in synthesis, a TRP-P-2 isomer that may have resulted from reaction of 2-methylpyridine as a contaminant of the 2,5-lutidine used as starting material, and an uncyclized precursor of TRP-P-1. All of the compounds were negative in the Ames mutagenicity test unless activated. The gamma-carbolines TRP-P-1 and TRP-P-2 were more active than the alpha-carbolines GLOB-P-1 and GLOB-P-2 in strains TA98 and TA100. All of the carbolines were more active in TA98 than in TA100. Among both GLOBs and TRPs, the less substituted compounds were more active in TA98. Activities of GLOBs and TRPs were approx equal in TA100. The methyl-substituted pyridoimidazole GLU-P-1 was more active than the unsubstituted GLU-P-2 in both tester strains. GLU-P-1 was the most active of the promutagens. High pressure liquid chromatographic retention vol and fluorescent parameters of the compounds are reported. (16 Refs)

50. EXAMINATION OF CHILI PEPPER AND NUTMEG OLEORESINS USING THE SALMONELLA/MAMMALIAN MICROSOME MUTAGENICITY ASSAY.

Buchanan RL, Goldstein S, Budroe JD
Dept. Nutrition and Food Sciences, Drexel Univ., Philadelphia, PA, 19104
J Food Sci; 47(1):330-331,333 1982

Past investigations have suggested that various arylalkene spice compounds warrant further study as possible naturally occurring mutagens and/or carcinogens. The present study carried out a detailed examination of nutmeg oleoresin, myristicin, chili pepper oleoresin, capsaicin, and vanillylamine for in vitro mutagenicity using the Salmonella/mammalian microsome mutagenicity assay. None of the materials tested displayed significant mutagenicity over a wide range of concentrations. (Author abstract) (43 Refs)

51. THE MUTAGENICITY OF LACTARIUS MUSHROOMS.

Knuutinen J, Von Wright A
Food Res. Lab., Technical Res. Centre Finland, Biologinkuja 1, SF 02150 Espoo 15, Finland
Mutat Res; 103(2):115-118 1982

Mushrooms of four species of Lactarius (necator, torminosus, helvus, rufus) collected in southern Finland were tested for mutagenicity. The Ames test was performed with Salmonella typhimurium strains TA 100 and TA 98 and liver homogenates prepared from phenobarbital-induced NMRI mice (Oy Orion Ab). Extracts of all the mushroom species showed mutagenic activity at 2-6 times the spontaneous background level. The addition of S9 metabolic activation mix did not enhance mutagenic activity, and indeed decreased it slightly in two species. Histidine levels in the mushrooms were not the cause of mutagenesis; in fact the extract of the species with the lowest histidine content (L necator) had the greatest mutagenic activity. The mutagenic material is resistant to at least short periods of boiling, ruling out very thermolabile or volatile compounds, thus making the public health problem more urgent. (7 Refs)

52. STUDIES TO EVALUATE ARTIFICIAL SWEETENERS, ESPECIALLY REMSEN-FAHLBERG SACCHARIN, AND THEIR POSSIBLE IMPURITIES, FOR POTENTIAL MUTAGENICITY BY THE SALMONELLA/MAMMALIAN LIVER MICROSOME TEST.

Herbold BA
Inst. Toxicology, Bayer AG, Postfach 101709, D-5600 Wuppertal 1, W. Germany
Mutat Res; 90(4):365-372 1981

Mutagenic activity (MA) of artificial sweeteners and some possible impurities of artificial sweeteners was studied in Salmonella typhimurium with or without metabolic activation by S9. S9 was prepared from livers of Sprague-Dawley rats. Bacterial cultures were exposed to saccharin (Sacc: less than or equal to 12,500 ug/plate), o-toluene sulfonamide or p-toluene sulfonamide (less than or equal to 18,000 ug/plate), o-sulfamoylbenzoic acid, p-sulfamoylbenzoic acid, o-sulfobenzoic acid, p-sulfobenzoic acid, phthalimide, anthranilic acid, disulfide salt, boiled saccharin, or one of three saccharin extracts (all less than or equal to 2,500 ug/plate), cyclamate (less than or equal to 12,500 ug/plate), or cyclohexylamine (less than or equal to 2,500 ug/plate). Cyclophosphamide (less than or equal to 100 ug/plate) and trypaflavine (less than or equal to 200 ug/plate) were used as positive controls. All Sacc tested was prepared by the Remsen-Fahlberg process. With the exception of one Sacc extract, all chemicals tested were negative for MA in the standard Ames assay. One organic extract of Sacc produced inconclusive results in three consecutive experiments. Results indicate that neither Sacc, cyclamate, cyclohexylamine, nor known impurities of the sweeteners are mutagenic in the Salmonella/mammalian liver microsome test. (23 Refs)

53. MUTAGENICITY OF THE ANTIPARASITIC DRUG VERMOX FOR SALMONELLA TYPHIMURIUM HISTESTER STRAINS.

Paulikova H, Dobias L
Regional Hygienic Inst., 728 92 Ostrava, Czechoslovakia
Mutat Res; 90(4):463-468 1981

Salmonella typhimurium strains TA100, TA98, TA1535, and TA 1538 were exposed to Vermox to test the mutagenicity (MG) of methyl-5(6)-benzoyl-2-benzimidazole carbamate, a component of Vermox. No MG as indicated by histidine prototrophic reversion was noted with or without metabolic activation by rat liver S9. Blood samples from rats treated with Vermox did not produce an increase in reversions, indicating that metabolic activation in vivo does not produce mutagenic activity. (11 Refs)

54. LACK OF MUTAGENICITY OF THE FUNGICIDE 2,4,5,6-TETRACHLOROISOPHTHALONITRILE IN THE AMES SALMONELLA/MICROSOME TEST.

Wei CI
Dept. Food Science and Human Nutrition, Univ. Florida, Gainesville, FL, 32611
Appl Environ Microbiol; 43(1):252-254 1982

The fungicide 2,4,5,6-tetrachloroisophthalonitrile was found to be not mutagenic to five Salmonella typhimurium tester strains. Incorporation of either a liver or a kidney activation system did not increase the mutagenic activity of the fungicide. (Author abstract) (14 Refs)

55. MUTAGENICITY OF STYRENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

de Meester C, Duverger-van Bogaert M, Lambotte-Vandepaer M, Mercier M, Poncelet F
Unite TBCM, Sch. Pharmacy, Univ. Louvain, UCL/72.37, 72, Ave. E. Mounier, B-1200 Brussels, Belgium
Mutat Res; 90(4):443-450 1981

Seven strains of Salmonella typhimurium were exposed to gaseous styrene. Styrene produced mutagenic effects in strains TA1530, TA1535, and TA100; mutagenesis required the presence of S9 from rats treated with Aroclor. A dose-effect relationship was established in TA1530. Mutagenic activity of styrene was weak. Results indicate formation of a volatile, unidentified intermediate compound by S9 enzymes. (22 Refs)

56. MUTAGENICITY OF RUBBER VULCANIZATION GASES IN SALMONELLA TYPHIMURIUM.

Hedenstedt A, Ramel C, Wachtmeister CA
Wallenberg Lab., Univ. Stockholm, S-106-91 Stockholm, Sweden
J Toxicol Environ Health; 8(5/6):805-814 1981

The effect of changes in stock composition and thermal treatment of vulcanization gases was investigated by means of short term mutagenicity tests. Vulcanization fumes from a styrene-butadiene rubber produced a significant increase in mutations when compared to control tests. Pyrolysis gases from a peroxide cured butadiene acrylonitrile rubber had no mutagenic effect, but were markedly more toxic than the other polymers tested. Magnesium oxide cured chloroprene rubber than a direct mutagenic effect. Sulfur and peroxide cured ethylene propylene rubbers both showed a mutagenic effect. Temperature apparently affects the type of compound released and the resulting mutagenicity. (18 Refs)

57. PATULIN AND RUBRATOXIN B: INTERACTIONS OF TOXIC AND HEPATIC EFFECTS AND MUTAGENIC POTENTIAL.

Kangsadalampai K, Salunkhe DK, Sharma RP
Interdepartmental Toxicology Program, Utah State Univ., Logan, UT, 84322
J Food Prot; 44(1):39-42,54 1981

Toxicities of patulin and rubratoxin B were studied in male Fischer rats in terms of synergistic or antagonistic effect through the determination of mixed function oxidase levels, mortality rates, and alterations of liver and body wt. The Salmonella/microsome assay was also used as an additional indicator for mutagenicity. Antagonistic interactions between the mycotoxins were shown on mortality rate, body wt, and enzyme level. Individual mycotoxins or their combinations were not mutagenic in the Ames test. (22 Refs)

58. EFFECT OF AROMATIC HYDROCARBONS ON THE METABOLISM OF 2-AMINOANTHRACENE TO MUTAGENIC PRODUCTS IN THE AMES ASSAY.

Kawalek JC, Andrews AW
Bureau Veterinary Medicine, Food and Drug Admin., Beltsville, MD, 20705
Carcinogenesis; 2(12):1367-1369 1981

When the carcinogen 2-aminoanthracene was tested for mutagenicity in the Ames assay, the inclusion of aromatic hydrocarbons of various ring sizes had differing effects on mutagenicity depending on the components of the assay. (Author abstract) (16 Refs)

59. MUTAGENICITY OF DIPHENYLHYDANTOIN AND SOME OF ITS METABOLITES TOWARDS SALMONELLA TYPHIMURIUM STRAINS.

Sezzano P, Raimondi A, Arboix M, Pantarotto C
(c/o Pantarotto), Istituto di Richerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157, Italy
Mutat Res; 103(3-6):219-228 1982

The mutagenicity of 5,5-diphenyl-hydantoin (DPH) and its major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) were tested in vitro using S typhimurium strains TA1535, TA100, TA1537, TA1538, and TA98. Neither DPH nor HPPH alone was mutagenic or cytotoxic at doses ranging from 1-1000 ug/plate. When mutagenicity was tested in the presence of liver S9 fraction from rats pretreated with different cytochrome P-450/448 inducers (corn oil; phenobarbital (PB)); beta-naphthoflavone; 3-methylcholanthrene 3-MC; Aroclor 1254, (PCB), DPH at concentrations of 25 ug/plate with 3-MC and 250 ug/plate with PCB pretreated rat S9 had limited mutagenic activity in strain TA 1538. Significant increases in revertant colonies were found with HPPH tested on strains TA98, TA1535, TA1537, and TA1538 when in the presence of S9 from BNF-, 3MC- and especially PCB-pretreated rats. These results are further supported by metabolic studies, which showed that HPPH and the other DPH metabolite 5-(3,4-dihydroxyphenyl)-5-phenylhydantoin (DHP) were formed when incubation of DPH was done in S9 fractions from livers of rats pretreated with BNF, 3MC or PCB, but not PB. Epoxide intermediates in the metabolism of DPH to HPPH and to HPPH to DHP may be responsible for the mutagenicity. A reaction mechanism is proposed. (21 Refs)

60. URINE-MEDIATED AMES TEST: INTERACTIONS.

Aeschbacher HU, Ruch E
Res. Dept., Nestle Products Technical Assistance Co. Ltd., CH-1350 Orbe, Switzerland
Mutat Res; 103(2):127-131 1982

The vol of urine extracted for use with the Ames test for mutagenicity has an important influence on the results. Urine collected from six human subjects (who neither smoked, nor consumed alcohol or stimulatory beverages, nor medicines) was combined; half of the pooled urine was subjected to beta-glucuronidase (BG) enhancement for 24 hr at 37 C, while the other half was stored at 4 C. Volumes of 0.5, 1.5, and 3.0 liters were passed through 14.5 x 3.5 cm plastic columns containing purified XAD-2 resin. Dimethyl sulfoxide-dissolved residues were added to plates of Salmonella TA98 in amounts from 25-100 ul, and mutagenicity scored by number of revertants in two series: one with 2-acetylaminofluorene (2AF) and S9 activation and one with daunomycin (DM) but no S9. Mutagenicity was inhibited in a volume-dependent way in both series, and was more pronounced for the BG-treated urine. When urine extracts from urine without BG enhancement were plated with the mutagens (2AF and DM) the inhibitory effect occurred only with the extract from the highest vol of urine (3 liters). (8 Refs)

61. URINARY METABOLITES OF 3,3'-DICHLOROBENZIDINE AND THEIR MUTAGENICITY.

Tanaka KI
Toray Shiga Hosp., 7-35, Sonoyama 2-chome, Otsu 520, Japan
Sangyo Igaku; 23(4):426-427 1981

3,3'-dichlorobenzidine (DCBZ) was administered to rats, urinary metabolites of the DCBZ, 3,3'-dichloro-N-acetylbenzidine (N-AcDCBZ) and 3,3'-dichloro-N,N'-diacetylbenzidine (NN'-AcDCBZ), were observed in the urine of the rats, and mutagenicity of the DCBZ, N-AcDCBZ, and NN'-AcDCBZ was investigated using Salmonella typhimurium TA 98 and TA 100 and a revertant mutagenicity test. Spectrographic pure DCBZ was administered po (20 mg) to five rats (Group 1), per trachea (10 mg) to five (Group 2), and pc (200 mg) to five (Group 3); five rats were not administered the DCBZ. DCBZ, N-AcDCBZ, and NN'-AcDCBZ were detected with both gas chromatography and high pressure liquid chromatography in the urine of Group 1 and 2 rats. Only NN'-AcDNBZ was observed in the urine of Group 3 rats. With the aid of Ames test, mutagenic activity of 1 ml urine samples containing N-acetyl DCBZ metabolites was shown to increase with the concentration of the metabolites in the urine samples from the Group 1 and 2 rats, but no mutagenic activity was observed for the 1 ml samples from the Group 3 rats. The mutagenic activity of the NN'-AcDCBZ was much lower than that of the DCBZ or the N-AcDCBZ. These techniques were thought to be applicable for study of mechanisms of carcinogenicity of these metabolites as well as for biological monitoring of the substances. (7 Refs) (In JPN)

62. LIGHT-ENHANCED GENETIC TOXICITY OF CRYSTAL VIOLET.

Levin DE, Lovely TJ, Klekowski E
Biochemistry Dept., Univ. California, Berkeley, CA, 94720
Mutat Res; 103(3-6):283-288 1982

The light-enhanced genetic toxicity of crystal violet (CV) and the effect of Aroclor 1254-induced rat-liver S9 fraction on its genetic toxicity in the Rosenkranz (Escherichia coli polymerase A-) assay and the Ames (Salmonella TA98, TA100, and TA1537) test were studied. The Rosenkranz assay showed a dark-incubation genotoxic effect of CV, which was enhanced under light incubation. The presence of S9 had no effect on the genetic toxicity of CV in the Rosenkranz assay. In the Ames assay CV exhibited no mutagenic activity in any strain; CV at 5.0 ug/plate sterilized the plates under dark incubation, and this effect was enhanced under light incubation. S9 whether enzymatically active, thermally inactivated, or not buffered, eliminated the toxicity of CV for the strains of Salmonella. The nutritive value of S9 or a possible binding of CV to S9 proteins, are suggested as possible explanations for the protective activity of S9 when its enzymatic activity is destroyed. (12 Refs)

63. UKEMS TRIAL: BACTERIAL MUTATION TESTS OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL, AND BENZYL CHLORIDE, USING E. COLI WP2UVRA(PKM101) AND S. TYPHIMURIUM TA98 AND TA100.

Venitt S, Crofton-Sleigh C, Bosworth DA
Pollards Wood Res. Station, Chester Beatty Res. Inst., Inst. Cancer Res., Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Mutat Res; 100(1-4):39-43 1982

Mutagenicity plate tests using Escherichia coli WP2uvrA(pKM101) and Salmonella typhimurium TA98 and TA100 were performed on 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). 4CMB was tested in WP2uvrA(pKM101) using the microtiter fluctuation test. In the plate tests, 4CMB was reproducibly mutagenic to all three strains, BC was reproducibly mutagenic to TA100 and WP2uvrA(pKM101), and 4HMB was uniformly negative in all three strains. Fluctuation tests indicated that 4CMB ages in dimethylsulfoxide solutions even when kept frozen. (4 Refs)

64. MUTAGENICITY OF 4-CHLOROMETHYLBIPEHNYL (4CMB) TO E. COLI WP2 UVRA PKM101.

Penman MG
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr. Macclesfield, Cheshire, England
Mutat Res; 100(1-4):15-16 1982

An Escherichia coli (strain WP2 uvrA pKM101) plate-incorporation assay was used to test the mutagenicity of the potential carcinogen 4-chloromethylbiphenyl (4CMB). A positive response was observed in the absence of S9, with a max response at 500 ug/plate. (1 Ref)

65. MUTAGEN AND ANTI-MUTAGEN IN GINGER, ZINGIBER OFFICINALE.

Nakamura H, Yamamoto T
Biological Inst., Konan Univ., Kobe 658, Japan
Mutat Res; 103(2):119-126 1982

Rhizome juice of ginger contains compounds that both enhance and suppress the mutagenic action of 2(2-furyl)-3-(5-nitro-2-furyl)acryl amide (AF2) and N-methyl-N'-nitro-N-nitrosoguanidine (NTG) on Escherichia coli B/r (strain Hs30). The clear supernatant of filtered, centrifuged mashed rhizome increased the apparent mutagenic effects of AF2 and NTG as determined by reversions to arginine independence of E coli. Diethyl ether extraction of ginger juice, followed by chromatographic separation and mutagenicity tests, revealed that the factor enhancing mutagenesis by AF2 was (6)-gingerol. The same compound also enhanced NTG mutagenicity, and caused reversions and death of bacteria in a concentration-dependent way. The water-soluble and boundary fractions of an ether/water separation of ginger rhizome juice suppressed the mutagenesis of (6)-gingerol, which remained in the ether fraction. It is suggested that (6)-gingerol may be activated by specific mutagens only, which explains why antimutagenic agents in the rhizome juice were effective in some experiments and not in others. (10 Refs)

66. ANTIMUTAGENIC ACTIVITIES OF HUMAN PLACENTAL EXTRACT ON ULTRAVIOLET LIGHT- AND GAMMA-RAY-INDUCED MUTATION IN ESCHERICHIA COLI WP 2 B/R TRP.

Kada T, Mochizuki H
Dept. Induced Mutation, National Inst. Genetics, Mishima, Shizuoka-ken 411, Japan
J Radiat Res (Tokyo); 22(3):297-302 1981

Antimutagenic activities of human cells on radiation-induced cellular mutagenesis were studied. The Escherichia coli strain WP2 B/r trp was used. A germicidal lamp was used for UV irradiation of a cold suspension of bacteria in phosphate buffer solution. Gamma-ray irradiation with a 137Cs source at a dose rate of 33 kilorad/hr was performed on bacterial cells kept in ice-water. Experiments were performed to confirm that the reduction of induced trp positive (Trp+) colonies results from antimutagenic effects during radiation-induced mutagenesis. The sensitivity of Trp+ clones to human placental extract was studied under conditions comparable to those of the antimutagenicity assay. Results showed that the number of induced mutant colonies decreased significantly with UV- and gamma-irradiation; effects of placental extract on the survival of Trp+ colonies were not as significant. The extract is not mutagenic, and results indicate that it contains factors which antagonize UV- or gamma-ray-induced mutations in bacteria. Results of reconstruction experiments show that the Trp+ cells are not particularly sensitive to the placental extract on UV- or gamma-ray induction. Human placental extract apparently works not on the expressed Trp+ mutant cells but rather in the course of mutagenesis. Presence of the antimutagenic factor in human placental tissues is of interest if it indeed reduces radiation-induced mutations in the embryo. (8 Refs)

67. ACTIVITY OF 4CMB AND 4HMB IN BACTERIAL MUTATION ASSAYS.

Lodge DC, Bootman J, May K
Life Science Res., Stock, Essex CM4 9PE, England
Mutat Res; 100(1-4):33-34 1982

Mutagenicities of 4-chloromethylbiphenyl (4CMB) and 4-hydroxymethylbiphenyl (4HMB) were determined in conventional pour-plate tests for chemical levels of 1.6-1,000 ug/plate. 4CMB was directly active in all tests, inducing both frameshift and base substitution mutations. Inclusion of S9 mix did not significantly affect 4CMB-induced responses. 4HMB was inactive in all experiments. (1 Ref)

68. THE MUTAGENICITY OF 4CMB IN A MICROWELL BACTERIAL FLUCTUATION TEST.

Styles J, Pritchard N
Central Toxicology Lab., Imperial Chemical Industries Ltd., Macclesfield, Cheshire, England
Mutat Res; 100(1-4):71-73 1982

Microwell bacterial fluctuation test responses for 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) are described. 4CMB and BC were both positive in the presence or absence of S9 mix, although displacement of the dose-response curve was observed when S9 mix was used. 4HMB gave negative results with or without S9 mix. The results indicated that 4CMB is a direct-acting bacterial mutagen. (4 Refs)

69. THE GENETIC TOXICOLOGY IN FUNGI OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC). SURVEY OF THE RESULTS OF THE U.K.E.M.S. COLLABORATIVE GENOTOXICITY TRIAL 1981.

Parry JM, Wilcox P
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):185-200 1982

The genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) has been studied in Saccharomyces cerevisiae, Aspergillus nidulans and Neuropsora crassa. Both 4CMB and BC are potent mutagens for nuclear genes in N crassa. No conclusions have been drawn about the abilities of any of the three compounds to induce point mutations in A nidulans. Both 4CMB and BC are potent inducers of mitotic gene conversion and mitotic crossing-over in fungi. 4CMB and BC are able to induce mitotic crossing-over in both yeast and A nidulans; no such activity has been detected with 4HMB. 4CMB has appeared to be a potent point mutagen in S cerevisiae. 4HMB is effective in inducing mitochondrial mutations and inhibiting the activity of mitochondrial genome. Results of studies on the effects of BC and 4CMB on the mitochondrial genome have been variable. Overall, the results of fungal assays have indicated that both 4CMB and BC are genetically active chemicals; no such activity has been detectable with 4HMB. (17 Refs)

70. INDUCTION OF PETITE FORMATION IN SACCHAROMYCES CEREVISIAE BY EXPERIMENTAL ANTITUMOUR AGENTS. STRUCTURE-ACTIVITY RELATIONSHIPS FOR 9-ANILINOACRIDINES.

Ferguson LR, Baguley BC
Cancer Res. Lab., Univ. Auckland Medical Sch., Private Bag, Auckland, New Zealand
Mutat Res; 90(4):411-423 1981

Derivatives of 9-anilinoacridine (9AA) with unsubstituted or substituted acridine rings at the 3 and/or 6 position were tested for inhibition of growth of L1210 murine leukemia cells in vitro and induction of respiration-deficient (petite) mutations in D5 diploid Saccharomyces cerevisiae. D5 cells were exposed to test compounds in growth and nongrowth conditions. Comparison of the effects of the petite-inducers ethidium (ETH) and proflavine (PRO) showed that ETH converted at least 99% of D5 cultures to petite over a wide range of doses; PRO did not exceed 90% at any dose level. PRO produced petites at doses 120x those of ETH and only at cytotoxic doses. Tests of petite induction (PI) by various 9AA showed three classes of compounds: inactive, ETH-like, and PRO-like. The existence of two active classes suggests that two different targets involving DNA mediate the effects of 9AA. At least one acridinyl amino group was required for induction of petites. Amino groups increased DNA binding. Small anilino substituents on 3-amino-9AA produced PI similar to that of PRO; larger substituents abolished all PI. 3,6-Diamino 9AA had PI similar to that of ETH. Max PI did not correspond to max inhibition of L1210 cells. Results indicate that DNA binding and biological activity in both D5 and L1020 systems are related to the size of anilino substituents. (18 Refs)

71. ASSAY OF THE INDUCTION OF MITOTIC CROSSING-OVER AND ANEUPLOIDY IN YEAST BY BC, 4CMB AND 4HMB.

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):139-143 1982

Abilities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over and mitotic chromosome aneuploidy were assayed in strain D6 of Saccharomyces cerevisiae. Only BC and 4CMB produced mitotic crossing-over. Addition of S9 mix reduced the toxicity and genetic activity of both compounds. Neither 4CMB, 4HMB, nor BC induced mitotic chromosome aneuploidy. (3 Refs)

72. THE INDUCTION OF MITOTIC GENE CONVERSION IN THE YEAST, SACCHAROMYCES CEREVISIAE JD1 BY 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB).

Brooks TM, Gonzalez LP
Sittingbourne Res. Centre, Shell Res. Ltd., Kent ME9 8AG, England
Mutat Res; 100(1-4):157-162 1982

Mitotic gene conversion induced by 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) was scored in log-phase and stationary-phase cultures of Saccharomyces cerevisiae JD1. Both 4CMB and BC induced mitotic gene conversion, particularly in stationary-phase cells. 4HMB showed no activity in either of the assays. (2 Refs)

73. ACTIVITY OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE IN ASSAYS FOR GENE CONVERSION AND PETITE INDUCTION IN SACCHAROMYCES CEREVISIAE STRAIN D4.

Mitchell IG, Gilbert PJ
Medicinal Res. Centre, Beecham Pharmaceuticals Res. Div., The Pinnacles, Harlow, Essex, England
Mutat Res; 100(1-4):169-172 1982

Gene conversion (GC) and petite induction (PI) in Saccharomyces cerevisiae strain D4 were assessed for their ability to correctly identify the carcinogenic and mutagenic potential of three chemical analogs: 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). PI tests detected only the mutagenicity of BC and were highly variable. GC assays were highly reproducible and indicated the mutagenicity of 4CMB and lack of mutagenicity of 4HMB. GC assays failed to distinguish the potency of 4CMB from that of BC. (5 Refs)

74. MITOCHONDRIAL TOXICITY IN SACCHAROMYCES AS A MEASURE OF CARCINOGENICITY.

Patel R, Wilkie D
Dept. Botany and Microbiology, Univ. Coll., London, England
Mutat Res; 100(1-4):179-183 1982

Primary antimitochondrial activities of 4-chloromethylbiphenyl (4CMB), benzyl chloride, and 4-hydroxymethylbiphenyl (4HMB) were identified by selective inhibition of cell growth in non-fermentable medium, induction of the mitochondrial mutation petite, and selective blockage of mitochondrial protein synthesis. Only the biphenyls appeared to be carcinogenic based on their antimitochondrial activity; neither can be considered a potent carcinogen and 4CMB appears weaker than 4HMB. (2 Refs)

75. TESTING FOR MITOTIC CROSSING-OVER AND INDUCED ANEUPLOIDY USING ASPERGILLUS NIDULANS AS PART OF THE UKEMS TEST PROGRAMME.

Watkins P
Pharmaceuticals Div., Imperial Chemical Industries Ltd., Mereside, Alderly Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):133-138 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over in a diploid strain of Aspergillus nidulans (strain P), heterozygous for the gene determining resistance to p-fluorophenylalanine, were studied in selective media. 4CMB gave clear indication of the induction of crossing-over with increases over the length of t he pre-incubation period. Inclusion of S9 mix reduced the effect. BC produced a small induction of crossing-over clearly noticeable only when the conidia were treated after 5 and 6 hr of incubation. 4HMB did not show any positive response in the assay. (4 Refs)

76. ASPERGILLUS NIDULANS AS A TEST ORGANISM FOR CHEMICAL MUTAGENS.

Igwe CN, Cohn P
Sch. Engineering and Science, Polytechnic Central London, 115 New Cavendish St., London W1R 8AL, England
Mutat Res; 100(1-4):127-131 1982

Effects of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) on survival, mitotic segregation, mitotic gene conversion, and point mutations in three strains of Aspergillus nidulans were studied. BC had the greatest effect and 4HMB the least on survival and gene conversion in a diploid strain and point mutation in a haploid strain. Neither 4CMB, 4HMB, nor BC had any effect on mitotic segregation. (4 Refs)

77. THE TESTING OF 4CMB, 4HMB, AND BC FOR MUTAGENICITY IN A NEW NEUROSPORA CRASSA HETEROKARYON.

Luker MA
Inst. Animal Genetics, Edinburgh Univ., West Mains Road, Edinburgh EH9 3JN, Scotland
Mutat Res; 100(1-4):123-126 1982

Neither 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), nor benzyl chloride (BC) produced a dose response for mutation induction in the Neurospora crassa heterokaryon. The three compounds were therefore not mutagenic according to the test, although 4CMB, 4HMB, and BC did induce an increase in mutation frequency above control levels. Only the lower doses (150 ug/ml) of 4CMB and 4HMB in suspension treatments had any biological effect. Growing cells were more sensitive to 4CMB and 4HMB than were resting conidia, but 4HMB showed no mutagenic activity. Both BC and 4CMB produced dose-response data for ad+ and pFPA-R mutation induction and were regarded as mutagenic. (no Refs)

78. CHARACTERIZATION OF POLYCYCLIC KETONES AND QUINONES IN DIESEL EMISSION PARTICULATES BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY.

Choudhury DR
Vick Div. Res. and Development, Richardson-Vicks Incorporated, 1 Bradford Road, Mount Vernon, NY, 10553
Environ Sci Technol; 16(2):102-106 1982

High-resolution gas chromatography/mass spectrometry was used to determine the chemical composition of two highly mutagenic subfractions of the neutral fraction of a diesel particulate extract. Diesel emission particulates were collected from a Volkswagon Rabbit by the dilution tunnel method and the two subfractions were isolated by silica gel chromatographic fractionation of the neutral extract. Of seven subfractions prepared, subfractions 4 and 5 had the highest specific mutagenicity in the Ames Salmonella mutagenesis assay, with subfraction 4 accounting for 52% of the direct-acting mutagenicity and subfraction 5, 13%. Both direct-acting mutagens and promutagens which required metabolic activation were found in the subfractions. Elution patterns suggested that the subfractions contained compounds more polar than parent and alkyl-substituted polycyclic aromatic hydrocarbons. Ketone, quinone, carboxaldehyde, and hydroxy derivatives and their alkyl homologues were characterized. The single largest family of compounds detected were 9-fluorenone and its C1-C4 alkyl homologues. The mutagenicity of most of the compounds identified is unknown. (18 Refs)

79. CHARACTERIZATION, BIOLOGIC ACTIVITY AND MUTAGENICITY OF PROTEIN FROM CIGARETTE TOBACCO, SMOKE AND PIPE CONDENSATE (MEETING ABSTRACT).

Misconi LY, Steward AM
Swinburne Institute of Technology, Hawthorn, Victoria, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The proteins of several extracts of tobacco, smoke and smoke condensate, were examined by mol wt, isoelectric point, (pI), presence of subunits, mutation and immunogenecity. Total protein levels were determined by the Lowry method. The non-protein components were removed by dialysis and ultra-filtration. Hplc, (High pressure liquid chromatography), using TSK3000 SW column (Beckman), resolved high and low mol wt proteins. The solvent system used was 0.2M Na2SO4, 0.01M Na-PO4 buffer pH 6.5, the flow rate was 0.5-1.0 ml/min. The linear relationship between elution vol and mol wt of standard globular proteins allowed determination of mol wt. Up to 12 different proteins were identified by SDS-PAGE (sodium dodecyl sulfate - polyacrylamide gel electrophoresis and mercaptoethanol, which ranged between 20,000-150,000 daltons. This separation had the advantages of mol wt determination and the possible fractionation of the highest mol wt protein into its smaller subunits. When the highest mol wt band (150,000) was reapplied to a fresh SDS-PAGE, two bands were obtained of MW 150,000 and 85,000: when the latter band alone was applied to SDS-PAGE, both hands again appeared, suggesting the existence of aggregates. Dh skin activity was confined to these larger MW bands. Isoelectric focusing was performed using LKB Ampholine pH 3-11 PAGE gels. The focusing pattern demonstrated pI values (4.3-5.8) and the ampholyte mixture exhibited a linear pH profile. The Salmonella/mammalian-microsome mutagenicity test (Ames Assay-TA98 and TA100) with and without metabolic activation was applied to protein fractions obtained from tobacco, smoke and pipe smoke condensate, and significant mutagenic activity was detected. (no Refs)

CYTOGENETIC TESTS

80. SISTER-CHROMATID EXCHANGES INDUCED BY SOME CHROMIUM COMPOUNDS IN HUMAN LYMPHOCYTES IN VITRO.

Gomez-Arroyo S, Altamirano M, Villalobos-Pietrini
Laboratorio de Citogenetica y Mutagenesis Ambiental, Universidad Nacional Autono ma de Mexico 20, Centro de Ciencias de la Atmosfera, DF, Mexico
Mutat Res; 90(4):425-431 1981

Human lymphocytes were treated with K2Cr2O7 (0.025-0.1 ug/ml),CaCrO4 (0.01-0.02 ug/ml), or CrO3 (0.025-0.1 ug/ml) in the presence of 5-bromodeoxyuridine for two replicative cycles. All three test compounds increased the occurrence of sister chromatid exchanges (SCE) in a dose-dependent manner, as detected by a combination of fluorescent and Giemsa staining methods. Compounds containing Cr++++++ were effective in producing SCE in the order CaCr04 greater than CrO3 greater than K2Cr2O7. (50 Refs)

81. SISTER-CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Jenkinson PC, Smith KL
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England
Mutat Res; 100(1-4):301-304 1982

Induction of sister chromatid exchanges (SCE) in human lymphocytes by exposure to noninhibitory doses of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was studied. 4CMB produced significant increases in frequency of SCE. BC produced increases that were just barely significant. Results suggest that SCE assay may be a more accurate test of mutagenicity in human lymphocytes than chromosome breakage assay. (3 Refs)

82. DECREASED RATE OF BENZO(A)PYRENE-INDUCED SISTER CHROMATID EXCHANGE IN FIBROBLAST CULTURES FROM PATIENTS WITH LUNG CANCER.

Rudiger HW, Harder W, Maack P, Kohl FV, Schmidt-Preuss U
Dept. Medicine I, Univ. Hamburg, Martinistr. 52, D-2000 Hamburg 20, W. Germany
J Cancer Res Clin Oncol; 102(2):169-175 1981

Fibroblast cultures from 29 lung cancer patients including 9 familial cases and from 25 healthy controls were investigated. We studied the benzpyrene-induced sister chromatid exchange (SCE) following incubation in the presence of 150 nM benzo(a)pyrene and found spontaneously increased SCE values in the patients' cells but a reduced response to benzpyrene as compared to the control cultures. The benzpyrene-induced SCE was positively correlated with both benzpyrene metabolism and DNA adducts in normal control cells but not in the patients' cells. The ratio of benzpyrene DNA adducts and benzpyrene-induced rate of SCE calculated for the individual cell strains exhibited a bimodal distribution with patients' cells, but not with control cells. We speculate that the described differences between patients' and control fibroblasts might reflect a genetic predisposition to the development of lung cancer in about one half of the patients tested. (Author abstract) (10 Refs)

83. INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN DIPLOID FIBROBLASTS BY MUTAGENS WITH AND WITHOUT RAT LIVER MICROSOMAL ACTIVATION.

Yang DP, Graupensperger F, Minecci LC, Rubin BA

Wyeth Laboratories, Inc., PO Box 8299, Philadelphia, PA, 19101

Environ Mutagen; 3(1):45-52 1981

Effects of a promutagen, a plant clastogen, and two direct mutagens were tested on sister chromatid exchange (SCE) induction in WI-38 cells with and without rat liver microsomal activation. Exponentially growing cells, 24 hr after subcultivation were treated with cyclophosphamide (CY), maleic hydrazide (MH), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitro-quinoline-1-oxide (4NQO) at various concentrations in the growth medium at 37 C for 1 hr. The frequency of SCE was estimated by the 5-bromodeoxyuridine-dye technique with and without addition of rat liver microsomal suspension (S-9). CY concentrations from 1 x 10(-5) M to 1 x 10(-3) M with S-9 mix increased the number of SCE/cell in a dose-dependent manner. Without S-9 mix, CY concentrations less than 1 x 10(-3) M did not produce more SCE than the controls. MNNG at 1 x 10(-8) M and 4NQO at 1 x 10(-7) M without S-9 produced significant increases in SCE/cell. Addition of S-9 slightly decreased the effects of MNNG and 4NQO in the formation of SCE. MH was tested at pH 6.4 and pH 7.6. MH at 1 x 10(-3) M without S-9 mix inhibited cell multiplication at pH 7.6, but did not cause a significant increase in SCE/cell. No interactions were noted between MH (2 x 10(-4) M) and S-9 mix nor between MH and pH levels tested. Results indicate that in the presence of metabolic activation, SCE formation in human diploid fibroblasts in vitro may be used as a potential assay for mutagenicity. (35 Refs)

84. SISTER CHROMATID EXCHANGE (SCE) INDUCTION BY PROMUTAGENS IN CULTURED HUMAN HEPATOMA CELLS (MEETING ABSTRACT).

Abe S, Sasaki M, Nemoto N

Chromosome Research Unit Fac Sci, Hokkaido University, Sapporo, Japan

Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Cultured human hepatoma Hc-1 and Hc-4 cells were shown to produce an increased frequency of SCEs after treatment with benzo(a)pyrene (BP). Analysis of metabolism of BP by high pressure liquid chromatography indicated that Hc-1 and Hc-4 cells produce various kinds of BP metabolites including 7,8-dihydrodiol, a precursor of the ultimate metabolite of BP, which is supposedly responsible for induction of SCEs. Several other kinds of aromatic hydrocarbons, aflatoxin B1 and cyclophosphamide also induced SCEs in Hc-1 and Hc-4 cells. The findings suggest that Hc-1 and Hc-4 cells could convert a wide range of promutagens into active metabolites to induce SCEs, and may serve as simple in vitro screening systems for promutagens without exogenous activation systems. (no Refs)

85. ALTERATIONS IN THE FREQUENCY OF SISTER CHROMATID EXCHANGES IN FLATFISH FROM PUGET SOUND, WASHINGTON, FOLLOWING EXPERIMENTAL AND NATURAL EXPOSURE TO MUTAGENIC CHEMICALS.

Stromberg PT, Landolt ML, Kocan RM

Office Marine Pollution Assessment, Natl. Oceanic and Atmospheric Admin., Boulder, CO

Alterations in the Frequency of Sister Chromatid Exchanges in Flatfish from Puget Sound, Washington, Following Experimental and Natural Exposure to Mutagenic Chemicals. Available from National Technical Information Service, Springfield, VA, as PB82-124637:, 53 pp., 1981.

Contamination of the aquatic environment by chemical pollutants has become a serious environmental problem which is heightened by the fact that a number of these contaminants have been demonstrated to be mutagenic or carcinogenic. In the present study the technique of sister chromatid exchanges (SCE) was applied to English sole (Parophrys vetulus) collected from Puget Sound, Washington. SCE were observed 5.5 days after in vivo exposure to a thymidine analogue, bromodeoxyuridine which allows for differentiation in the staining affinity of chromatids and visualization of exchanges between them. To test the efficacy of this technique as a useful tool in screening fish for evidence of exposure to mutagenic chemicals, the chromosomes of English sole from a polluted site were examined and found to have a significantly higher SCE rate than in the baseline. This study showed that the technique of SCE could be successfully applied to a marine fish species and that the effects of low concentrations of mutagens could be detected using this method. (Author abstract)

86. THE KILLIFISH NOTHOBRANCHIUS RACHOWI, A NEW ANIMAL IN GENETIC TOXICOLOGY.

van der Hoeven JC, Bruggeman IM, Alink GM, Koeman JH

Dept. Toxicology, Agricultural Univ., De Dreijen 12, Wageningen, The Netherlands

Mutat Res; 97(1):35-42 1982

The use of Nothobranchius rachowi (Cyprinodontidae) in a sister-chromatid exchange (SCE) test is described and compared with SCE results obtained with Umbra pygmaea. N rachowi was treated with 5-bromo-2'-deoxyuridine (BrdU) by placing 150 mg/liter of the compound directly into the tap water in the aquarium; U pygmaea received BrdU injections (0.5 mg/g ip). Gill tissue cell suspensions from both fish were examined for SCE following 70 hr exposure to ethylmethane sulfonate (EMS: 24-120 ug/ml) in the aquarium water, and N rachowi was also exposed for 50 hr in a similar fashion to cyclophosphamide (CP: 2.5-50.0 ug/ml). Both fish showed concentration-dependent SCE responses to EMS; N rachowi exhibited dose-dependent response to CP, which indicated that CP was almost 3x as effective an inducer of SCEs as EMS. Advantages of N rachowi over U pygmaea in SCE tests include possible larger number of metaphases per specimen, more rapid testing, potential for laboratory rearing of fish, and 16 vs 22 chromosomes. A disadvantage of N rachowi is its requirement for warmer water (25-27 C vs 20 C). (10 Refs)

87. ACTIVATED OXYGEN SPECIES AT THE ORIGIN OF CHROMOSOME BREAKAGE AND SISTER-CHROMATID EXCHANGES.

Emerit I, Keck M, Levy A, Feingold J, Michelson AM

Laboratoire de Cytogenetique Experimentale, Institut Medical des Cordeliers, Universite Paris VI, 15, Rue de l'Ecole de Medecine, Paris 6eme, France

Mutat Res; 103(2):165-172 1982

The effect of free superoxide anion radicals produced by the xanthine oxidase system in causing chromosome breaks and rearrangements, plus increased sister chromatid exchanges (SCE), in human lymphocytes is compared with the results of those produced by photoreduction of flavine mononucleotide by near-UV radiation. The protective influence of superoxide dismutase (SOD) was also tested. Both methods of free radical generation caused chromosome aberrations, mainly chromatid breaks (50%) and gaps (28%), and SCE, which could be prevented with SOD. (22 Refs)

88. NORMAL SISTER-CHROMATID EXCHANGES IN ORAL CONTRACEPTIVE USERS.

Husum B, Wulf HC, Niebuhr E

Dept. Anaesthesia, Rigshospitclet, Copenhagen, Denmark

Mutat Res; 103(2):161-164 1982

A group (A) of 63 women (15-42 yr old; av 22.3) who used no medication whatsoever was compared with a second group (B) of 52 women (16-43 yr old; av 26.3) who used oral contraceptives (OC; combinations of progestins and estrogens) with respect to the effect of cigarette smoking on sister chromatid exchanges (SCE) in peripheral lymphocytes. Mean numbers of SCE/cell ranged from 8.42-9.52 for group A, and 8.54-10.36 for group B, over a range of cigarette use of 0-greater than 20/day. The total number of SCE in 30 metaphases of each woman was transformed from an assumed Poisson distribution to a normal distribution, and a linear regression and Bartlett's test were performed which gave independent estimates of basic variance summed as 4.43 for group A and 5.97 for group B. It was concluded that use of OC does not influence SCE in lymphocytes in either smoking or nonsmoking women. (8 Refs)

89. SISTER-CHROMATID EXCHANGE IN PATIENTS WITH HEPATITIS.

Ghosh PK

Dept. Anthropology, Univ. Delhi, Delhi-110 007, India

Mutat Res; 103(3-6):303-306 1982

The lymphocytes of 28 adult patients, 12 of whom had virus 'A' and 16 of whom had virus 'B' hepatitis as determined by serum antigen tests, were examined for sister-chromatid exchanges (SCEs) induced by bromodeoxyuridine (10 ug/ml). Patients with virus 'A' hepatitis had a mean SCE/cell of 8.61 +-2.21, those with virus 'B' had a mean SCE/cell of 10.12 +-2.83; 20 control patients' lymphocytes averaged 5.21 +-1.26 SCE/cell. After complete chemical and biochemical recovery, 2/6 of the virus 'A' hepatitis patients and 1/5 of the virus 'B' hepatitis patients had reduced SCEs, although not to levels equivalent to controls. Failure of SCE levels to return to control levels may have been due to the presence of the not replaced virally-affected lymphocytes still in the system after the patients had recovered. (17 Refs)

90. METAPHASE ANALYSIS OF HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Smith KL, Jenkinson PC

Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England

Mutat Res; 100(1-4):297-299 1982

Chromosome mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was assayed in lymphocytes from a healthy human donor. Mitosis was inhibited by 4CMB at concentrations greater than 20 ug/ml and by BC at concentrations greater than 10 ug/ml. At lower concentrations neither compound increased the number of cells showing chromosome breaks or the number of breaks/cell. 4CMB increased gaps at 10 ug/ml. Results indicate that neither 4CMB nor BC is mutagenic in human lymphocytes. (2 Refs)

91. ELIMINATION OF RADIATION-INDUCED CHROMOSOME ABERRATIONS IN A CULTURE OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES. I. FREQUENCY OF ABERRATIONS IN THE FIRST AND IN THE SECOND MITOSES.

Piatkin EK, Nugis VIu

Inst. Biophysics, Moscow, USSR

Tsitologiia; 23(11):1310-1316 1981

The frequency of radiation-induced chromosome aberrations was studied in human peripheral blood lymphocytes irradiated with 60Co gamma rays (100-500 rads). Irradiated cells were incubated with broxuridine for 58-66 hr, and the chromosome aberrations in the first and second mitoses were assessed by the harlequin staining. For all radiation dosages tested, the frequency of chromosome aberrations in the first mitosis was 1.6-2x greater than that in the second mitosis. (15 Refs) (In RUS)

92. CHROMOSOME ANALYSIS OF CULTURED RAT-LIVER EPITHELIAL CELLS (RL4) TREATED WITH 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE.

Malallah G, Danford N, Parry JM

Genetic Toxicology Group, Univ. Coll. Swansea, Swansea SA2 8PP, Wales

Mutat Res; 100(1-4):279-282 1982

Induction of chromosomal aberrations by 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in rat-liver epithelial cells of the line RL4, which retains some metabolic activation. Cytotoxicity was determined by seeding 50,000 cells/well onto culture plates, culturing for 24 hr, and then exposing the cells to a test chemical for 24 hr. The concentration of test chemical producing 50% inhibition of cell growth (GI50) was calculated for each chemical. Genotoxicity assays were conducted using 25, 50, 75, and 100% of the GI50. Cell cultures were exposed for 24 hr to 6, 12, 18, or 24 ug 4CMB/ml, 25, 50, 75, or 100 ug 4HMB/ml, or 7.5, 15, 22.5, or 30 ug BC/ml. Both 4CMB and BC produced significant increases in chromosomal aberrations at doses that were only slightly toxic to RL4 cells. Sixty uM 4CMB produced approx 6x as much damage as 60 uM BC; 120 uM 4CMB produced greater than 10x as much damage as 120 uM BC. 4CMB produced 3x as much chromosome damage as equitoxic concentrations of BC. No clear effects on chromosome number were noted, except an increase in the number of cells with 43 or fewer chromosomes at 18 or 24 ug/ml 4CMB.

Since no increase was observed in the number of cells with 46 or more chromosomes, 4CMB apparently does not cause nondisjunction. 4HMB produced no chromosomal aberrations. Results indicate that 4CMB and BC are clastogenic and 4CMB has the greater activity. (1 Ref)

93. CHROMOSOME-BREAKING ABILITY OF ARECOLINE, A MAJOR BETEL-NUT ALKALOID, IN MOUSE BONE-MARROW CELLS IN VIVO.

Panigrahi GB, Rao AR
Cancer Biology Lab., Sch. Life Sciences, Jawaharlal Nehru Univ., New Delhi - 110 067, India
Mutat Res; 103(2):197-204 1982

Arecoline (1,2,5,6-tetrahydro-1-methyl-3-pyridine carboxylic acid methyl ester), an ingredient of betel-quid, which is chewed commonly in Southeast Asia and the Western Pacific and has been associated with a high rate of oral cancer in these areas, was tested for in vivo chromosome breaking ability with Swiss albino mouse bone marrow. Commercial arecoline was administered by daily ip injection at concentrations of 2.0, 1.0, 0.5, and 0.25 mg per mouse and given for 10, 20, and 30 days for each dose. Aberrations in metaphase chromosomes were greatest at higher doses, and included chromatid and chromosome breaks, ring structures, multiple breaks, and pulverization of chromosomal elements. There was an inverse relationship between the duration of arecoline exposure (10, 20, or 30 days) and the magnitude of chromosome aberrations, which gradually declined as treatment time increased. Chromatid breaks was the only damage noted in control cells, which were treated with vehicle. (24 Refs)

94. MUTAGENIC EFFECTS OF COMBINATIONS OF CHEMICAL CARCINOGENS AND ENVIRONMENTAL POLLUTANTS IN MICE AS SHOWN BY THE MICRONUCLEUS TEST.

Watanabe M, Honda S, Hayashi M, Matsuda T
Dept. Community Medicine, Toyama Medical and Pharmaceutical Univ., Toyama, Japan
Mutat Res; 97(1):43-48 1982

Combinations of dimethylnitrosoamine (DMN) or N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) and CdCl2 or polychlorinated biphenyls (PCB) were force-fed to male ddY mice. The Schmidt method of determining polychromatic erythrocytes (PCEs) in bone marrow cells was used to measure mutagenicity. DMN alone gave a clear dose-dependent response, whereas Cd alone did not; Cd + DMN enhanced the PCE frequency over that for the equivalent concentration of DMN alone. Possible enhancement of MNNG effects by Cd was also observed. PCB alone had almost no effect, and no synergistic or additive effect with DMN or MNNG was seen. Corn oil seemed to inhibit DMN activity. The results suggest that some combinations of carcinogens and environmental pollutants can interact in mutagenic activity. (4 Refs)

95. IS 4CMB CLASTOGENIC IN VIVO? PRELIMINARY RESULTS FROM THE MOUSE TRANSPLACENTAL MICRONUCLEUS TEST.

Cole RJ, Cole J
Biology Div., Sussex Centre Medical Res., Univ. Sussex, Brighton, England
Mutat Res; 100(1-4):379-380 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB) was tested by a transplacental micronucleus assay in 'Porton' strain albino mice. 4CMB was injected ip at 0-250 mg/kg into pregnant mice on day 16 or 17 of pregnancy. Polychromatic RBC from fetal liver and neonatal mice were examined. 4CMB was highly toxic to fetuses but was not clastogenic. (2 Refs)

96. AN EVALUATION OF THE MUTAGENIC POTENTIAL OF 4-CHLOROMETHYLBIPHENYL (4CMB) USING THE MICRONUCLEUS TEST.

Richardson JC, Proudlock RJ, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):375-378 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was measured in COBS CD-1 (ICR) BR (ICR derived) mice. Test compounds were injected ip. None of the compounds produced any increase in frequency of micronuclei in polychromatic RBC. The highest dose of 4CMB did not affect the ratio normochromatic/polychromatic RBC. (10 Refs)

97. CYTOGENETIC EFFECTS OF BC AND 4CMB IN THE MOUSE EVALUATED BY THE MICRONUCLEUS TEST.

Hartley-Asp B
Pharmacology Dept., AB Leo Res. Lab., Box 941, S-251 09 Helsingborg, Sweden
Mutat Res; 100(1-4):373-374 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was measured in SPF NMRI female mice using the micronucleus assay. Various doses of the test compounds were injected ip in two fractions. 4CMB was 10x as toxic as BC in test animals. Neither compound increased the frequency of micronuclei in polychromatic erythrocytes. (no Refs)

98. ASSAY OF 4CMB, 4HMB, AND BC BY THE MICRONUCLEUS TEST: SUBCUTANEOUS ADMINISTRATION.

Scott K, Topham JC
Imperial Chemicals Ltd., Mereside, Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):365-371 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in (CBA x Balb/c)F1 mice. Test compounds were injected sc in doses up to the max tolerated dose of 4CMB and 4HMB and up to 2,000 mg/kg BC. None of the test compounds produced any increase in frequency of micronuclei in polychromatic erythrocytes. No mutagenicity was detected by this method. (2 Refs)

99. 4CMB: INVESTIGATION OF ACTIVITY IN A MOUSE MICRONUCLEUS TEST.

Whalley HE, Bootman J, Rees R
Life Science Res., Stock, Essex, England
Mutat Res; 100(1-4):361-364 1982

Mutagenic effects of 4-chloromethylbiphenyl (4CMB) were studied in vivo in CD-1 mice. 4CMB was injected ip daily for 5 days at doses up to lethal levels. Toxicity of 4CMB was greater in females than in males. 4CMB produced no increase in the occurrence of micronuclei of polychromatic erythrocytes relative to controls. Results indicate no mutagenicity for 4CMB identifiable by this method. (2 Refs)

100. 4CMB, 4HMB, AND BC EVALUATED BY THE MICRONUCLEUS TEST USING A MULTIPLE SAMPLING METHOD.

Holmstrom M, McGregor DB, Willins MJ, Cuthbert JA, Carr S
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):357-359 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was measured in vivo in CD-1 male mice. Mice received test compounds po at various fractions of the LD50. The frequency of formation of micronuclei in polychromatic erythrocytes was determined at different sampling times. No mutagenicity was indicated for any of the test compounds by this method. (5 Refs)

101. THE EFFECTS OF 4CMB, 4HMB, AND BC IN THE MICRONUCLEUS TEST.

Danford N, Parry JM
Genetic Toxicology Res. Group, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):353-356 1982

The effects of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) on the micronuclei of polychromatic erythrocytes of male Tuck To outbred mice were studied in vivo. Test compounds were injected ip in one or two doses. None of the test compounds produced any increase in micronuclei in polychromatic erythrocytes. (3 Refs)

102. MICRONUCLEUS FORMATION COMPARED TO THE SURVIVAL RATE OF HUMAN MELANOMA CELLS AFTER X-RAY AND NEUTRON IRRADIATION AND HYPERTHERMIA.

van Beuningen D, Streffer C, Bertholdt G
Institut f. Med. Strahlenphysik und Strahlenbiologie, Univ.-Klinikum Essen, Hufelandstr. 55, D-4300 Essen 1, W. Germany
Strahlentherapie; 157(9):600-606 1981

After neutron and x-ray irradiation and combined x-ray irradiation and hyperthermia (3 hr, 42 C), the survival rate of human melanoma cells was measured by means of the colony formation test and compared to the formation of micronuclei. Neutrons had a stronger effect on the formation of micronuclei than the combination of x-rays and hyperthermia. X-rays had the lowest effect. The dose effect curve showed a break at that dose level at which a reduction of cells was observed in the cultures. A good relation between survival rate and formation of micronuclei was found for the x-ray irradiation, but not for the neutron irradiation and the combined treatment. These observations are discussed. At least for x-rays, the micronucleus test has turned out to be a good screening method for the radiosensitivity of a biologic system. (Author abstract) (15 Refs) (In GER)

103. MICRONUCLEUS TEST IN VICIA FABA ROOT TIPS TO DETECT MUTAGEN DAMAGE IN FRESH-WATE R POLLUTION.

Degrassi F, Rizzoni M
Institute Genetics, Faculty Sciences M.F.N., Univ. City, 00185 Rome, Italy
Mutat Res; 97(1):19-33 1982

The pattern of micronucleus frequency was compared with that of chromosome aberrations and mitotic anomalies in relation to mechanism of action of the mutagen, dose, exposure time, and time between treatment and fixing. Root tips were subjected to a range of doses of x-rays, mitomycin C, methyl methanesulfonate, ethidium bromide, or colchicine. All treatments caused dose-dependent responses, both in chromosome anomalies and micronucleus generation. Generally micronuclei-generating events were more frequent 2-3 cycles before the peak in micronuclei was apparent. Where short and long exposure times yielding the same total dose were used, the longer time was both more mutagenic and more toxic. Control levels of chromosomal and mitotic anomalies and micronuclei numbers were always low. Micronucleus frequency was directly proportional to mitotic index and to both chromosomal and mitoclastic generating events, regardless of the mechanism of action of the agent employed. Micronucleus frequency is a more sensitive indicator than frequency of generating events observed in mitosis, particularly with low doses and weak mutagens. (33 Refs)

104. ACQUIRED HEMATOLOGIC DISORDERS FOLLOWING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER (MEETING ABSTRACT).

Jochimsen P, Corder M, Patil S

Department of Surgery, University of Iowa, Iowa City, IA

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The development of acute bone marrow cancer following mastectomy and institution of alkylating agents as an adjuvant in two patients, led to the search for bone marrow cytogenetic abnormalities among 13 patients who had received such therapy, and were then compared with 8 others with a similar history of mastectomy for Stage II cancer, but who had not received chemotherapy. The 2 patients with acute leukemia were demonstrated to have an aneuploid condition along with structural rearrangements in chromosomes 11 and 12. No other evidence of chromosome aberrations were discovered in any of the other marrows examined whether or not alkylating agents had been utilized as an adjuvant. Perceiving that any induced abnormality might initially be more subtle and reflected in granulyte (polymorphonuclear, PMN) reserve, rather than chromosome morphology, the results of prednisolone stimulation tests in 16 patients, postmastectomy and 2 yr of alkylating adjuvant chemotherapy plus or minus antimetabolites, were compared with 13 normal women of similar age. Significant differences were observed in the initial total WBC, PMN count, leukocyte count, and hemoglobin level between the study group and controls. A significant chronic def ect in PMN circulating levels and in PMN's which can be mobilized from the marrow by glucocorticoids was demonstrated and indicates the long-term effect of adjuvant chemotherapy continues to be of concern. Whether the latter defect is related in any way with acute bone marrow malignancy requires further observation. (no Refs)

TESTS FOR DNA DAMAGE AND REPAIR

105. DNA DAMAGE AND ITS REPAIR IN HUMAN NORMAL OR XERODERMA PIGMENTOSUM FIBROBLASTS TREATED WITH 4-NITROQUINOLINE 1-OXIDE OR ITS 3-METHYL DERIVATIVE.

Mirzayans R, Waters R
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, England
Carcinogenesis; 2(12):1359-1362 1981

Normal human or excision deficient xeroderma pigmentosum (XP) fibroblasts were exposed to either the potent carcinogen 4-nitroquinoline 1-oxide (4NQO) or the weaker acting 3 methyl derivative of this compound. The inhibition of cell growth, DNA damage and DNA repair were then monitored in these cells. The data indicate that the modification of 4NQO by methylation actually changes the type and amount of DNA damage induced by this carcinogen. More specifically, the methylation of 4NQO at the three position prevented the formation of 4NQO induced DNA adducts manifesting themselves as alkaline stable lesions whose repair was cytosine arabinoside inhibitable in normal cells, but defective in excision deficient XP cells. Alkaline labile lesions induced by 4NQO which are repairable in the above XP cells were still induced by the 3 methyl derivative but a lower frequency on an equimolar basis. (Author abstract) (13 Refs)

106. DETECTION OF CHEMICAL CARCINOGENS BY ASSAY OF UNSCHEDULED DNA SYNTHESIS IN RAT TRACHEAL EPITHELIUM IN SHORT-TERM ORGAN CULTURE.

Ide F, Ishikawa T, Takayama S
Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
J Cancer Res Clin Oncol; 102(2):115-126 1981

A short-term organ culture of rat tracheal epithelium was used to detect the ability of 53 chemicals to induce UDS. In this system all direct-acting compounds (ultimate or proximate carcinogens) tested induced UDS. Of 24 compounds requiring metabolism (procarcinogens), nine induced UDS, viz, 4NQO, AF-2, BP, DMN, DEN, and NP. Urethane, AAF, and 2,7-AAF induced very slight UDS. 3-Methyl-4NQO for which carcinogenicity data is incomplete was positive in our system. Among the cancer chemotherapeutic agents tested only mitomycin C induced UDS. MC and DMBA, which are known to induce cancer of respiratory organs in experimental animals, and DAB, aflatoxin B1 and Trp-P-1, which are strong carcinogens in the liver, did not induce UDS within 2 hr. With the longer exposure (24 hr), these carcinogens also failed to elicit UDS. All the carcinogens that induce UDS showed clear dose-dependent effects. No non-carcinogens tested induced UDS. These results suggested that this system should be useful for screening environmental chemicals suspected of damaging DNA of the respiratory organ on the basis of organotropic effects of UDS induction in cultured rat tracheal epithelium. (Author abstract) (54 Refs)

107. AN INVESTIGATION OF DNA-REPAIR PHENOMENA INDUCED BY 4-CHLOROMETHYLBIPHENYL (4CMB).

Pearson CM, Edwards K
Central Toxicology Lab., Imperial Chemical Industries, Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):211-214 1982

Ability of 4-chloromethylbiphenyl (4CMB) to induce phenomena associated with DNA damage and its repair were studied in cultured HeLa cells with assays of strand breakage, unscheduled DNA synthesis (UDS), and repair replication. A dose-related positive effect was observed for strand breaks, with 250 ug/ml showing a significant amount of 3H-DNA loss from the filter. The assays of UDS or repair replication showed no increase in thymidine incorporation above control levels and therefore no repair synthesis. Repair replication at doses of 100 ug/ml 4CMB exhibited an inhibition of thymidine incorporation into DNA compared to controls. (3 Refs)

108. ROLE OF GUT FLORA IN THE GENOTOXICITY OF DINITROTOLUENE.

Mirsalis JC, Hamm TE, Sherill JM, Butterworth BE
Biochemical Genetics Dept., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Nature; 295(5847):322-323 1982

Role of intestinal microflora in dinitrotoluene (DNT) genotoxicity was studied using in vivo - in vitro hepatocyte DNA repair assay. A group of germ-free (axenic) and of associated with Charles River Altered Schaedler Flora (CRASF) male Fischer-344 rats were given 100 mg/kg sterile DNT by gavage in sterile corn oil. Rats associated with CRASF showed marked increase in unscheduled DNA synthesis (UDS) in hepatocytes after DNT treatment, whereas axenic rats showed no increase in UDS. Large increase in UDS was induced by dimethylnitrosamine given as positive control to rats, confirming the ability of axenic animals to carry out excision repair of DNA after exposure to cytotoxic agents. The cecal contents of each rat were cultured to confirm its bacterial status; those of the associated animals contained the complete CRASF flora. Several of the non-associated animals were found to be contaminated with one or two bacterial strains. Non-associated rats contaminated with Streptococcus faecalis showed a small increase in UDS after DNT treatment, while non-associated rats contaminated with Clostridium perfringens showed no increase. None of the contaminants were CRASF constituents. The absence of UDS in axenic animals indicates that metabolism of DNT by gut flora is a necessary step in the genotoxicity of DNT and indicates the value of the assay in assessing the carcinogenic potential of nitroaromatic compounds. (16 Refs)

109. DNA DAMAGE INDUCED BY THE ANTIHISTAMINIC DRUG METHAPYRILENE HYDROCHLORIDE.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Mutat Res; 103(3-6):213-218 1982

Methapyrilene hydrochloride (MH) added to the medium stimulated DNA-repair synthesis in cultured hepatocytes from adult male Holtzman rats. The effect was dose dependent over the range 10(-2)-10(-6) M, with a peak at 10(-3) M. Of more than 30 compounds tested by this protocol only known carcinogens and UV irradiation have been shown to produce more DNA damage than MH. MH treatment of hepatocytes for 30, 90, and 180 min clearly decreased the sedimentation velocity of hepatocellular DNA on alkaline sucrose gradients, indicating the formation of alkaline-labile lesions. The present evidence, when considered in light of recent studies demonstrating the tumor-inducing ability of MH in rats lead to the conclusion the MH is a complete carcinogen. (10 Refs)

110. DNA REPAIR STUDIES ON DIALLATE, TRIALLATE AND SULFALLATE IN HUMAN CELL CULTURES.

Benigni R, Dogliotti E, Falcone E, Calcagnile A
Laboratorio di Tossicologia, Istituto Superiore di Sanita, Roma, Italy
Mutat Res; 103(3):385-390 1982

Induced unscheduled DNA synthesis (UDS) was measured in cells of the EUE line of epithelial-like cells by (3H)thymidine autoradiography and (3H)thymidine/(14C)thymidine incorporation ratio determined after scintillation counting. Autoradiography studies showed that the structurally related carbamates diallate, triallate, and sulfallate caused a significant, dose-dependent increase in UDS over the range of 10(-6) -10(-4) M, with dose-dependent inhibition at 10(-3) and 10(-2) M. No such effect was observed in the 3H/14C assay although treatment with N-methyl-N'-nitro-nitrosoguanidine and methylmethane sulfonate increased (3H)thymidine incorporation. The present results extend to human cells the suggested mutagenicity and carcinogenicity of these pesticides, which had been previously demonstrated in fungal and animal systems. (12 Refs)

111. DNA DAMAGE IN LIVER OF MICE TREATED WITH N-NITRODIMETHYLAMINE.

Pala M, Russo P, Nicolo G, Santi L, Parodi S
Istituto Scientifico per lo Studio e la Cura dei Tumori, Genoa, Italy
Mutat Res; 103(3-6):207-211 1982

N-Nitrodimethylamine (ip 225-900 mg/kg) caused DNA damage in vivo in the livers of 2 to 3-mo-old Swiss mice as determined by alkaline elution assay. DNA damage was evidently dose-dependent; the level of damage peaked at 4 hr posttreatment, with damage reduced to control levels 3 days after a single injection. (8 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

112. LIVER-MICROSOME S9 ENZYME INCREASES SPONTANEOUS BACKGROUND MUTATION FREQUENCY IN THE AMES SALMONELLA TEST SYSTEM IN THE ABSENCE OF ANY ADDED MUTAGEN.

Peak MJ, Dornfeld SS, Venters D
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Mutat Res; 103(3-6):263-265 1982

The number of spontaneous reversions of Salmonella typhimurium TA98 to prototrophy was measured 290 times, including 231 assays with 20, 50, and 50 ul/plate of Aroclor 1254-induced rat-liver S9 preparation. Numbers of spontaneous revertants in S9-treated plates were about 30% above the control for all three concentrations, and the differences were highly significant. Possible mechanisms suggested include S9 activation of some component in the plating medium or the presence of a nutrient in the S9. (3 Refs)

113. USE OF A RAT/HAMSTER S-9 MIXTURE IN THE AMES MUTAGENICITY ASSAY.

Weinstein D, Katz M, Kazmer S
Hoffmann-La Roche Inc., Bldg. 100, Nutley, NJ, 07110
Environ Mutagen; 3(1):1-9 1981

Mutagenicity of phenacetin, 2-aminoanthracene (2AA), 1,2-epoxybutane, and nitrosopiperidine was tested using liver S-9 from Sprague-Dawley male rats and male Syrian golden hamsters. Prior studies with phenacetin have shown that the standard Ames test induced with rat S-9 is negative, while with hamster S-9 it is positive. The use of a mixture of rat and hamster liver homogenates does not inhibit the ability to cause a mutagenic effect with phenacetin. The effectivness of rat S-9 to activate low concentrations of 2AA to mutagenicity for strains TA 1535, TA 100, and TA 1537 is not inhibited by mixing with hamster S-9. 2AA concentration of 0.10 ug/plate was mutagenic with rat S-9 alone or the mixture for strains TA 1535, TA 100, and TA 98. A low concentration of 0.25 ug/plate with strain TA 1537 was also mutagenic with rat S-9 alone or the mixture. The mutagenicity of the weak mutagen epoxybutane is similar with rat S-9 and rat/hamster S-9. The mixture causes more pronounced mutagenicity by nitrosopiperidine than rat S-9 alone. The mixture was comparable to the rat S-9 alone indicating that replacing rat S-9 with a rat/hamster S-9 mixture in the standard Ames test could increase the sensitivity of the test without interfering with rat S-9 activity. (18 Refs)

114. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

Raineri R, Poiley JA, Pienta RJ, AndrewsAW
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 21701
Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)-induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from rats were more active than those from hamsters when using BP. With the aromatic amines (AAF and AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and AC-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rats, which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

115. AGE-RELATED CHANGES IN MUTAGEN ACTIVATION BY RAT TISSUES.

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(c/o Birnbaum) Environmental Biology Branch, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Chem Biol Interact; 38(2):243-252 1982

Age-related changes in drug metabolism of the liver, lung and kidney of adult female Long-Evans rats were determined by measuring changes in mutagen formation. Activation of aflatoxin B1 (AFB1), 2-aminofluorene (AF) and 2-acetylaminofluorene (AAF) to mutagenic derivatives was assayed using the Ames Salmonella test system. The promutagens were incubated with tissue fractions from rats ranging in age from 2.5 to 25 mo. With all three compounds, hepatic, renal and pulmonary activation was lower in the senescent than in the young adult animals. The largest decrease, however, occurred prior to middle-age, ie before 9-13 mo. In liver and kidney, little change was detectable between the middle-aged and the old (20-25 mo) animals. However, pulmonary metabolism in the oldest animals was slightly higher than in the extracts from the middle-aged rats. The observed decline in mutagen activation may thus be a function of maturation rather than senescence. (Author abstract) (30 Refs)

116. IN VITRO MUTAGENIC ACTIVATION OF 3'-HYDROXY-METHYL-N,N-DIMETHYL-4-AMINOAZOBENZENE (3'-CH2OH-DAB) (MEETING ABSTRACT).

Mori Y, Niwa T, Toyoshi K
Gifu Univercity, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 198 1, Sapporo, Japan. The Association 415 pp., 1981.

Our earlier experiment indicates that 3'-CH2OH-DAB, a new potent hepatocarcinogen, showed mutagenic activity towards Salmonella typhimurium TA98 and TA100 when tested with S-9. In order to clarify the mechanism of metabolic activation by S-9, effects of various factors known to influence xenobiotics metabolism on the mutagenic activities of 3'-CH(2)0H-DAB and 3'-Me-DAB were studied. The pretreatment of rats with polychlorinated biphenyl (PCB) and 3-methylcholanthrene (3-MC) and sodium phenobarbital (PB) showed that the ability of S-9 to activate these compounds was induced to the highest extent by PCB followed by 3-MC and PB, and the activation reaction required NADPH as a cofactor. On the other hand, these compounds showed less or no mutagenic activity in the presence of the S-105 fraction or S-9 from the livers of non-treated rats, those of mice and hamsters, and other organs of rats. These results indicate that microsomal enzymes in the S-9 fraction of rat liver is responsible for the metabolic activation of 3'-CH(2)0H-DAB and 3'-Me-DAB and that the carcinogenic specificity in regard to organs and species is similarly observed in their mutagenic effects with S-9. (no Refs)

117. THE EFFECT OF TESTOSTERONE TREATMENT ON THE ABILITY OF FEMALE RAT LIVER S9 TO ACTIVATE AFLATOXIN B1 AND 2-AMINOFLUORENE IN THE AMES/SALMONELLA SYSTEM.

Chernesky P, Jayaraj A, Richardson A
Dept. Chemistry, Illinois State Univ., Normal, IL, 61761
Mutat Res; 103(3-6):267-273 1982

The activation of aflatoxin B1 (AFB1) and 2-aminofluorene (2AF) by liver homogenates (S9) from untreated and testosterone-treated female Fischer F344 rats was compared using the Ames Salmonella (TA98)/microsome assay. Testosterone treatment resulted in a 93% increase in the ability of S9 to convert AFB1 to mutagenic compounds in the Ames test and a 43% increase in the similar activation of 2AF. (21 Refs)

118. PROMOTION BY POLYCHLORINATED BIPHENYLS OF ENZYME-ALTERED FOCI IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U.S. Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45267
Cancer Lett; 15(2):185-190 1982

The number of gamma-glutamyltranspeptidase (GGTase)-positive foci was examined in livers of partially hepatectomized male Sprague-Dawley rats given an initiating dose of diethylnitrosamine (DENA: 0.3 millimole/kg body wt, po) followed 7, 28, or 49 days later by one to three doses of Aroclor 1254 (500 mg/kg, ip). Rats were killed 21 days after the last dose of Aroclor. Incidence of GGTase-positive foci increased from a mean of 0.70 foci/square cm (cm2) liver in solvent (tricaprylin)-treated, partially-hepatectomized, DENA-initiated controls to 2.28 foci/cm2 in animals given a single dose of Arocl or 1254. Maximum enhancement was obtained after two doses, which resulted in 3.47 foci/cm2. Up to three doses of Aroclor did not increase the incidence of GGTase-positive foci in partially-hepatectomized animals that had not received DENA. Aroclor 1254 appears suitable as an inexpensive promotor in a short-term initiation/promotion assay for chemical carcinogens. (20 Refs)

COMPARATIVE TEST RESULTS

119. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
Div. Toxicology, Lilly Res. Laboratories, Greenfield, IN, 46140
Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate carcinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally realted noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

120. THE EFFECTS OF 4CMB, 4HMB, AND BC ON SCE, CHROMOSOME ABERRATION AND POINT MUTATION IN CULTURED CHINESE HAMSTER OVARY CELLS.

Phillips BJ, James TE
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Mutat Res; 100(1-4):263-269 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in vitro in Chinese hamster ovary (CHO-KI-BH4) cells in the absence of exogenous metabolic activation systems. CHO-KI-BH4 cells were exposed to 4CMB, 4HMB, or BC for 2 hr. Tests of relative plating efficiency indicated that 4HMB is nontoxic at concentrations up to 100 ug/ml; above 100 ug/ ml 4HMB precipitated from soln. 4CMB was slightly more toxic than BC. Sister chromatid exchanges (SCE) were significantly increased by BC in a dose-related manner; the max effect of 4CMB was a doubling of the background frequency of SCE at a concentration of 7 ug 4CMB/ml; 4HMB had no effect on the frequency of SCE. 4CMB produced moderate but significant chromosomal aberrations (CA) within a concentration range of 10-20 ug/ml; BC produced somewhat more CA but at higher doses than 4CMB. 4HMB produced no effect on CA. 4CMB produced a slight increase in the frequency of cell mutations (CM) within a narrow range of doses around 10 ug/ml, BC produced a small increase at a dose of 18 ug/ml, and 4HMB had no effect on CM. Results indicate that 4CMB and BC are weakly mutagenic in the absence of an exogenous metabolic activation system. SCE, CA, and CM test results agreed quantitatively and qualitatively. (4 Refs)

121. DNA-DAMAGING ACTIVITY IN VIVO AND BACTERIAL MUTAGENICITY OF SIXTEEN AROMATIC AMINES AND AZO-DERIVATIVES, AS RELATED QUANTITATIVELY TO THEIR CARCINOGENICITY.

Parodi S, Taningher M, Russo P, Pala M, Tamaro M, Monti-Bragadin C
Dept. Oncology, Genoa Univ., Genoa, Italy
Carcinogenesis; 2(12):1317-1326 1981

Sixteen aromatic amines and azo-derivatives were studied. They were: benzidine; 2-acetylaminofluorene; 3'-methyl-p-dimethylaminobenzene; o-aminoazo-toluene; p-dimethylaminoazobenzene; 2,4-diaminotoluene; 4,4'-oxydianiline; 2,4-diaminoanisole; 4,4'-methylenedianiline; 2-naphthylamine; Auramine O; Rhodamine B; Ponceau MX; 1-naphthylamine; p-aminoazobenzene and aniline. The compounds were examined for their capability to induce alkaline DNA fragmentation in rat liver after treatment in vivo, for their mutagenicity in the Salmonella strains TA 98 and TA 100, for their acute toxicity and for their carcinogenicity in mice and rats. For each parameter a quantitative potency index was established, and the correlation existing amongst the different parameters investigated. Only mutagenicity in the strain TA 98 was slightly correlated with carcinogenic potency (r = 0.408). DNA fragmentation and toxicity were not correlated with carcinogenicity. A significant correlation was found between DNA fragmentation and toxicity (r = 0.539). No correlation was found between DNA fragmentation and mutagenicity. The lack of correlation between DNA fragmentation and carcinogenicity is in contrast with previous results obtained with a family of hydrazine derivatives and a group of nitroso compounds. For these two groups of chemicals correlation between DNA fragmentation and carcinogenicity existed, but not between carcinogenicity and mutagenicity in the Ames' test. It is suggested that short term tests can perform very differently for different classes of chemicals. (Author abstract) (22 Refs)

122. THE MUTAGENICITY OF DIALKYLAMINOALKYL CHLORIDES IN A BATTERY OF SHORT-TERM ASSAY S.

Thompson CZ, Rinzel SM, Probst GS, McMahon RE
Lilly Res. Laboratories, 307 E. McCarty St., Indianapolis, IN, 46285
Environ Mutagen; 3(1):33-43 1981

A battery of four short-term tests was employed in the study of dialkylaminoalkyl chlorides (DAAC). All DAAC compounds were screened by the concentration gradient technique for their ability to produce an increase in revertants in any of 10 bacterial strains used in the assay. The concentration gradient results were supplemented by determination of concentration-response relationships (Ames test) in the appropriate tester strains. Two additional tests performed were for chemically induced DNA repair in rat hepatocyte primary cultures (HPC-DNA repair) and for mutation at the thymidine kinase locus in the L5178Y mouse lymphoma cell. There was good correlation between results of the gradient plate test and the Ames test. DAAC were active in all test systems. Relative mutagenic potencies of the ethyl chlorides were similar in the bacterial tests and the L5178Y cell assay. Dialkylaminopropyl chlorides (DAAP) were weakly mutagenic in two Salmonella strains but were inactive in other test systems. Results with dialkylaminoethyl compounds suggest that if these agents which can form the aziridinium ion were evaluated in in vivo tests some would be found to be carcinogenic. Data on DAAP indicate that they have a low carcinogenic potential. (9 Refs)

123. MUTAGENICITY AND CHEMICAL ANALYSIS OF ALIPHATIC AND AROMATIC FRACTIONS OF PRUDHOE BAY CRUDE OIL AND FUEL OIL NO. 2.

Ellenton JA, Hallett DJ
Dept. of the Environment, Wildlife Toxicology Div., Natl. Wildlife Res. Center, Ottawa, Ontario K1A OE7, Canada
J Toxicol Environ Health; 8(5/6):959-972 1981

Chemical analyses of aliphatic and aromatic fractions of Prudhoe Bay crude (PBC) oil and fuel oil number 2 and their potential mutagenicity were investigated. Fraction 1 of both oils exhibited no mutagenic activity. PBC oil fractions 3 and 4 and fuel oil number 2 fraction 4 produced weak mutagenic activity with metabolic activation. A significant increase in sister chromatid exchanges occurred after treatment with various concentrations of fraction 3 and 4 from each oil. These results indicate genetic activity residing in the polycyclic aromatic hydrocarbon containing fractions of the tested oils in both bacteria and mammalian cells. (20 Refs)

124. ABSENCE OF MUTAGENIC AND CLASTOGENIC ACTION OF PINE-TAR RESIN IN THE SALMONELLA/ MICROSOMAL AND CHO CULTURE SYSTEMS.

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Inst. Biological Res., Natl. Hellenic Res. Foundation, 48, Vas. Constantinou Ave., Athens, Greece
Mutat Res; 103(3-6):229-232 1982

Salmonella typhimurium strains TA98 and TA100, with and without S9 mix prepared from livers of rats pretreated with Aroclor 1254, were subjected to doses of 0.1-4 mg/plate of the natural pine tar resin used in Greek 'retsina' wine in the Ames test. Sister-chromatid exchanges, chromatid abnormalities, and mitotic index were determined for Chinese hamster ovary cells (CHO) subjected to doses of 0.025-1 mg/ml of the same resin. Neither test indicated mutagenicity, but mitotic arrest of CHO cells was evident at all concentrations tested. (10 Refs)

125. GENOTOXICITY OF COCOA EXAMINED BY MICROBIAL AND MAMMALIAN SYSTEMS.

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Inst. Biochemistry, Federal Res. Centre for Nutrition, Engesserstr. 20, D-7500 Karlsruhe, W. Germany
Mutat Res; 103(3-6):275-281 1982

The bone marrow sister-chromatid exchange (SCE) test, performed with implanted 5-bromodeoxyuridine tablets; the micronucleus test performed with outbred 10 to 14 wk-old Chinese hamsters; and the Ames test with Salmonella typhimurium (strains TA1535, TA100, TA1537, TA1538, TA98) were used to evaluate the genotoxicity of cocoa and two of its constituents: theobromine (ThB) and caffeine (CA). Not roasted cocoa administered by stomach tube at doses of 0.1-0.6 g/animal caused a dose-dependent elevation of bone-marrow SCEs; roasted cocoa (chocolate liquor) gave almost identical results. Extraction of the fat (47% of cocoa) almost doubled the number of SCEs at the highest cocoa dose, to 10.01/cell, and increased the number of SCEs at all other doses somewhat less (range 5.33-7.88 SCEs/cell). Cocoa butter and ThB- and fat-free cocoa caused no significant elevation of SCEs. ThB alone at doses of 2.5-20 mg/animal, and ThB + CA (6:1) at the same doses caused similar high levels of SCEs (4.77-9.50) in a dose-dependent way. The micronucleus test was negative for roasted and fat-free cocoa, 0.6 g/animal, but highly positive for ThB (doses 2 x 20, 30, or 40 mg ThB), but ThB (dose 1 x 20, 30, or 40 mg/animal) gave negative results in the chromosome aberration test. None of the Salmonella strains showed any mutagenic effect of cocoa at concentrations of 5.0, 2.5, 1.0, and 0.5%; greater than or equal to 5.0% cocoa was antibacterial. ThB at 0.25% gave no evidence of mutagenicity with or without metabolic activation. ThB is evidently not demethylated in all mammals, and hence its non-mutagenicity cannot be assumed. (16 Refs)

126. MUTAGENICITY AND TOXICITY OF FUROCOUMARINS: COMPARATIVE INVESTIGATIONS IN 2 TEST SYSTEMS.

Abel G, Schimmer O
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Mutat Res; 90(4):451-461 1981

Photomutagenicity and phototoxicity of the linear furocoumarins 8-methoxypsoralen (8-MOP) and 8-isoamylenoxypsoralen (8-IOP) and of the angular furocoumarin 5'-methylangelicin (5-MA) were studied. Human peripheral lymphocytes (HPL) were cultured in the presence of 5-bromodeoxyuridine. At 47 hr the cultures were exposed to 8-MOP (21.6 ug/ml), 8-IOP (27.0 ug/ml), or 5-MA (20.0 ug/ml). At 48 hr the cultures were irradiated with UV-A. Cells were examined at 72 hr. 8-MOP and UV or 5-MA and UV produced significant increases in the frequency of sister chromatid exchanges (SCE) compared with controls. 8-MOP had the greatest effect, increasing SCE by a factor of 2. 8-IOP had no effect. 5-MA produced irregular results. Cultures of an arginine-dependent strain of Chlamydomonas reinhardii were exposed to the test compounds and immediately irradiated with UV-A. Equimolar concentrations of 8-MOP and 5-MA produced equal levels of toxicity. 8-IOP produced much less toxicity in a longer time period. 8-MOP produced the greatest mutation rate, as indicated by induction of Arg+ revertants. 8-IOP produced similar mutation rates but required 3x the UV-irradiation time. 5-MA was much less mutagenic. Results indicate that monofunctional furocoumarins present a smaller mutagenic hazard than bifunctional furocoumarins and should be preferentially tested for therapeutic efficiency. (26 Refs)

127. HARMAN AND NORHARMAN: INDUCTION OF SISTER-CHROMATID EXCHANGES IN HUMAN PERIPHERAL LYMPHOCYTES IN VITRO AND INTERACTION WITH ISOLATED DNA.

Madle E, Obe G, Hansen J, Ristow H
Institut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany
Mutat Res; 90(4):433-442 1981

The effects of harman, norharman, and derivatives of both compounds on human peripheral lymphocytes (HPL) in vitro and isolated DNA from calf thymus were studied. The frequency of sister chromatid exchanges in HPL was increased by harman or harman-derivatives but not by norharman or norharman-derivatives. Transcription of isolated DNA was inhibited by harman and to a lesser extent by norharman. In a filter binding assay harman bound DNA more strongly than norharman. (20 Refs)

128. MONITORING GENOTOXICITY IN THE OCCUPATIONAL ENVIRONMENT.

Sorsa M, Falck K, Norppa H, Vainio H
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):61-65 1981

The urinary mutagenicity assay and analysis of structural chromosome aberrations and sister chromatid exchanges in cultured lymphocytes were used to detect exposure to genotoxic chemicals in various job categories in the rubber industry and in oncology units at hospitals. The urine of workers in the rubber industry had significantly increased mutagenic activity after one week work in comparison to values obtained after vacation. Oncology nurses had a significantly higher mean sister chromatid exchange frequency than office personnel, but a value similar to that of other hospital nurses. (14 Refs)

129. POLYCYCLIC AROMATIC HYDROCARBONS AND POSSIBLE METABOLITES: CONVERTOGENIC ACTIVITY IN YEAST AND TUMOR INITIATING ACTIVITY IN MOUSE SKIN.

Siebert D, Marquardt H, Friesel H, Hecker E
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J Cancer Res Clin Oncol; 102(2):127-139 1981

The diploid respiratory-deficient strain of yeast D4-RDII was used to assay PAH and urethane as well as some oxygenated derivatives of PAH and the (aliphatic) epoxide hydrolase inhibitor TCPO for convertogenic (mutagenic) activity. As a positive control, the convertogenic ultimate rat liver carcinogen NOAcAAF was used. PAH and urethane were found inactive as convertogens, TCPO was weakly active, whereas oxygenated electrophilic derivatives of PAH, such as K-region oxides, were found strong convertogens. For comparison, some convertogenic key compounds were assayed for their tumor-initiating activity in mouse skin in the standardized system using TPA as a promoter. PAH were stronger initiators than all oxygenated derivatives of PAH tested. TCPO alone exhibited very weak, if any, initiating activity. It was unable to modify initiation to any significant extent, if administered 5 min prior to administration of an initiator. In the absence of correlation between convertogenic and initiating activity the question of the chemical nature of 'ultimate initiators' of mouse skin carcinogenesis awaits further investigation. (Author abstract) (35 Refs)

130. MUTAGENIC ACTIVITY OF TOMIZINE.

Gvazava EA, Revazova IuA, Radchenko LU, Bratslavskii VA, Oblapenko NG, Bobrinev EV
Res. Inst. Biological Testing of Chemical Compounds, Moscow Oblast', USSR
Khim Farm Zh; 15(11):31-34 1981

The activity of the antineoplastic agent tomizine (folic acid antagonist) was studied by means of various mutagenicity tests. The tomizine did not induce gene mutations in Salmonella, but increased the frequency of recessive lethal mutations in Drosophila. Exposure of male mice to the agent increased the frequency of dominant lethal mutations (15.5%, compared with 3.9% in control mice). The tomizine did not induce sister chromatid exchanges in human peripheral blood lymphocytes. (16 Refs) (In RUS)

131. PARAMECIUM TETRAURELIA. PRE-SCREEN FOR HAZARDOUS CHEMICALS: A RAPID-DETECTOR SYSTEM FOR HEALTH HAZARDS. PROGRESS REPORT.

Smith-Sonneborn J
Dept. Zoology and Physiology, Wyoming Univ., Laramie, WY
Paramecium Tetraurelia. Pre-Screen for Hazardous Chemicals: A Rapid-Detector System for Health Hazards. Progress Report. Available from National Technical Information Service, Springfield, VA, as DE81025884:, 18 pp., 1981.

Genotoxic and cytotoxic effects of dilutions of oil shale proces waters from three different retorting processes were evaluated using the Paramecium tetraurelia and the Salmonella assays. Process waters from above-ground, true in situ, and modified retorting process were analyzed. Significant mutagenicity was detected in waste water from both the above ground and true in situ retorting processes in both the Salmonella and Paramecium bioassays. The Salmonella assay required the addition of the rat liver S9 fraction; the Paramecium bioassay was more sensitive to genotoxic effects from an above-ground retort water without the addition of the rat liver fraction. Mutagenicity of the dilutions tested from the modified retort process was detected only in the Paramecium system The waste water from the above-ground retort process was the most toxic to both the protozoan and bacteria. Since the chemical composition of oil shale process waters can vary with: (1) the retorting process used, (2) the temperature of the retorting, (3) the composition of the shale rock, and (4) the sampling and storage procedures, the differences in biological activity observed between water can reflect differences in water contamination. (Author abstract)

132. TOXICOLOGIC EVALUATION OF BUMETANIDE, A POTENT DIURETIC AGENT.

McClain RM, Dammers KD
Dept. Toxicology and Pathology, Hoffmann-La Roche Inc., Nutley, NJ, 07110
J Clin Pharmacol; 21(11/12):543-554 1981

Preclinical toxicologic evaluations of bumetanide are presented. Teratogenic, mutagenic, and carcinogenic studies were performed. The results of reproduction and teratogenic tests with bumetanide showed no evidence of teratogenic effects. Bumetanide was not mutagenic in the Ames test. Apparent dose-related increase in the incidence of mammary adenomas observed in one long-term rat study was not confirmed in a repeated study. No significant increase in other types of tumors was observed in bumetanide-treated rats in either study. (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

133. UKEMS COLLABORATIVE GENOTOXICITY TRIAL: CYTOGENETIC TESTS OF 4CMB, BC AND 4HMB: SUMMARY AND APPRAISAL.

Scott D
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):313-331 1982

Studies of the genotoxic potential of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) in vitro and of 4CMB in vivo are reviewed. Trials used eight different systems (cultured rat-liver epithelial cells, Chinese hamster V79 and bone marrow cells, human lymphocytes and fibroblasts, and mouse bone marrow cells in vitro, and mouse spermatocytes and oocytes in vivo). Aberrations in chromosomal structure (CA) and sister chromatid exchanges (SCE) were produced by 4CMB and BC but not 4HMB. No consistent differences in effectiveness were found between 4CMB and BC. Changes in chromosome number were not produced by any of the test compounds. 4CMB produced greater increases in CA and SCE in the presence of metabolic activation systems (in rat liver epithelial cells or in the presence of S9 mix) than in the absence of such systems. Since 4CMB does not require activation, the findings suggest that under certain conditions 4CMB can be converted to a more potent electrophile. Overall results indicate that 4CMB is a weak mutagen. (16 Refs)

134. AN OVERVIEW OF THE CHEMICAL AND BIOLOGICAL REACTIVITY OF 4CMB AND STRUCTURALLY RELATED COMPOUNDS: POSSIBLE RELEVANCE TO THE OVERALL FINDINGS OF THE UKEMS 1981 STUDY.

Ashby J, Lefevre PA, Elliott BM, Styles JA
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):417-433 1982

Negative mutagenicity results for 4-chloromethylbiphenyl (4CMB) obtained during collaborative studies are discussed. Topics include bacterial mutagenicity of 4CMB with respect to structurally-related analogs of biphenyl, metabolic detoxification of 4CMB, the effect of 4CMB on thermal denaturation of calf thymus DNA, hydrolysis of 4CMB to 4-hydroxymethylbiphenyl (4HMB), activity of 4CMB relative to benzyl chloride (BC), detoxification of 4CMB by 'non-critical' macromolecules, and derivatives of 4CMB with altered chemical stability. Addition of a benzene ring to BC to yield 4CMB is apparently accompanied by a marked increase in genotoxic activity in vitro and a decrease in hydrolytic stability, such that 4CMB may be quickly transformed into 4HMB. Awareness of the hydrolytic stability of a new alkylating agent and knowledge of its aqueous/lipid partition coefficient, its stability in S9, and responses observed in a variety of modifications of the Salmonella assay are required for estimation of genotoxic potency in vivo. (19 Refs)

135. THE GENETIC TOXICOLOGY OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB), AND BENZYL CHLORIDE (BC) AS ASSESSED BY THE UKEMS GENOTOXICITY TRIAL (1981).

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):411-416 1982

Studies of the genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethybiphenyl (4HMB), and benzyl choride (BC) are reviewed. Bacterial studies showed that 4CMB is a strong, direct-acting mutagen. 4CMB produces frame-shift and base-pair mutations, apparently by different mechanisms. In fungi 4CMB produced point mutations, mitotic gene conversions, primary DNA damage, and mitotic crossing-over; the presence of metabolic activation systems (MAS) reduced overall toxicity without affecting genetic effects of 4CMB. In mammalian cell cultures 4CMB produced repairable DNA damage, point mutations, chromosome aberrations, and sister chromatid exchanges. In vivo studies did not show that 4CMB induces dominant lethal mutations, micronuclei, aberrations of sperm morphology, or skin tumors. Initial findings suggest that 4CMB may be a weak skin carcinogen. Bacterial studies showed BC to be mutagenic with approx 10 % of the base-pair substitution activity of 4CMB. The mutagenic activity of BC increased in the presence of MAS. In fungi BC had mutagenic activity similar to 4CMB. In mammalian cell cultures BC had approx 20% of the activity of 4CMB. No evidence of skin carcinogenicity has been found after 10 mo. No evidence for mutagenicity of 4HMB was found in any system tested. Overall results indicate the value of a range of tests in determining genetic toxicology of compounds. (8 Refs)

136. UKEMS GENOTOXICITY TRIAL 1981. IN VIVO ASSAY SYSTEMS.

Topham JC
Pharmaceuticals Div., Safety Medicines Dept., Imperial Chemical Industries Ltd., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):381-387 1982

In vivo studies of the mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) are reviewed. 4CMB was tested in 14 systems, 4HMB in 8 systems, and BC in 9 systems. All three compounds were tested by the micronucleus test (with administration po, ip, and sc), F1 sperm-head morphology test (with administration sc and ip), sex-linked recessive lethal test (SLRL), and somatic cell misregulation test (both by po administration). Only 4CMB was tested by the dominant lethal test and the transplacental micronucleus test in mice. Assays in mice did not yield positive results for any of the test compounds. All three compounds produced dose-related toxic effects in mice. 4CMB was more toxic in females than in males. SLRL in Drosophila melanogaster in different laboratories produced contradictory results: some marginally positive results for all three compounds could not be reproduced. Overall results indicate no mutagenicity in mice. No firm evidence of mutagenicity with SLRL was found. All three compounds showed positive results in somatic cell misregulation tests in D melanogaster. (1 Ref)

137. THE USE OF CULTURED MAMMALIAN CELLS IN THE UKEMS COLLABORATIVE GENOTOXICITY TRIAL (1981).

Arlett CF
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, East Sussex, England
Mutat Res; 100(1-4):271-276 1982

Genotoxicity trials of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4-HMB), and benzyl chloride (BC) are reviewed. The trials used cultures of cells from the mouse (cell line C3H/10T1/2 and lymphoma lines P388 and L5178Y), Chinese hamster (V79 male lung cells and ovary cells), and man (HeLa cells). Mutation test consistently indicated that 4CMB is mutagenic in the presence or absence of S9 mix. No mutagenic activity was found for 4HMB. BC was mutagenic in 3/4 studies, but the activity of BC could not be scaled to that of 4CMB. CMB was not mutagenic in the ouabain system, suggesting that 4CMB does not act as a frame-shift mutagen in mammalian cells. Studies of cell transformation produced conflicting results, particularly with the BHK transformation assay. DNA repair studies indicate that 4CMB is genotoxic while 4HMB is not. Contradictory results were reported for BC. Positive indications of mutagenicity were found in 17/26 tests of 4CMB, 2/16 tests of 4HMB, and 8/17 tests of BC. Results suggest that 4CMB is mutagenic while 4HMB is not; more studies are required to determine the mutagenicity of BC. (17 Refs)

138. SUMMARY OF EPA AND OTHER PROGRAMS ON THE POTENTIAL CARCINOGENICITY OF DIESEL EXHAUST.

Carey PM
Control Technology Assessment and Characterization Branch, Environmental Protection Agency, Ann Arbor, MI
Summary of EPA and Other Programs on the Potential Carcinogenicity of Diesel Exhaust. Available from National Technical Information Service, Springfield, VA, as PB82-128018:, 63 pp., 1981.

Much research has been performed to evaluate the health effects associated with exposure to diesel emissions. The research performed falls into five general areas: mutagenicity, carcinogenicity, non-genetic effects, characterization and epidemiology. EPA is conducting a massive research program that includes studies in each area. Since epidemiological data for diesel emissions are limited, a major portion of EPA's research effort involves determining the relative mutagenic and carcinogenic potency of diesel emissions compared to potencies of comparative emissions for which epidemiological data are available. EPA will use the results of these studies with epidemiological data for the comparative sources to assess the human health risk associated with exposure to diesel emissions. (Author abstract)

139. CARCINOGENIC EFFECTS OF COAL-CONVERSION MATERIALS.

Renne RA, Smith LG
Batelle Pacific Northwest Lab., Richland, WA
Carcinogenic Effects of Coal-Conversion Materials. Available from National Technical Information Service, Springfield, VA, as DE81028108:, 29 pp., 1981.

Tremendous expense and extensive time commitments are required for in vivo mammalian carcinogenesis tests. Regulatory agencies may not be completely satisfied without some repetition of the toxicity testing with the final product from the commercial plant. Nevertheless, I think the work that we are doing on these materials from the pilot and demo plants is valuable. We are attempting to determine the correlation between mutagenesis and carcinogenesis data on complex mixtures such as these synfuel materials. The heavy distillate that we are working with was highly mutagenic compared with the other materials tested in the Ames system; it was also highly carcinogenic in our mouse skin-painting assay. when we tested the fractions, we had somewhat different results from those of the mutagenesis assays: the basic fraction of the heavy distillate was highly mutagenic, but, at least now, it does not appear to be highly active in our mouse carcinogenesis assay. However, the basic tar and the neutral tar skin carcinogenesis data correlate fairly well with the mutagenesis data. The second point I would like to make is to emphasize the need for caution against depending heavily on equating PNA content with carcinogenic activity. I would like to point out that our data indicate that PNAs are not the only chemical group with which we should be concerned. We should also monitor for primary aromatic amines. Due to the concern inhalation of synfuels, we have begun inhalation studies on some of the SRC materials. (Author abstract)

140. RELATIONSHIPS BETWEEN CARCINOGENICITY, MUTAGENICITY, AND THEORETICAL REACTIVITY INDICES FOR POLYCYCLIC AROMATIC HYDROCARBONS.

Seybold PG, Vestewig R, Scribner JD
Dept. Chemistry and Biological Chemistry, Wright State Univ., Dayton, OH, 45435
Int J Quantum Chem Quantum Biol Symp; 8:401-408 1981

Results of a quantitative statistical study of correlations between carcinogenic activity, mutagenic activity, and the theoretical indices for a sample of polycyclic aromatic hydrocarbons and some methyl derivatives are presented. An objective comparison with alternative techniques suggests a usefulness in cancer prescreening procedures of potentially hazardous substances. (42 Refs)

141. TOXICOLOGY, INDUSTRIAL HYGIENE AND MEDICAL CONTROL OF TD1, MD1 AND PMPPI.

Woolrich PF
Upjohn Co., 7171 Portage Road, Kalamazoo, MI, 49001
Am Ind Hyg Assoc J; 43(2):89-97 1982

A comprehensive review of physiologic effects, toxicology, industrial hygiene, and medical control of isocyanates used to manufacture polyurethanes and polyisocyanurates is presented. The most significant effect of exposure to toluene diisocyanate (TDI), methyl bisphenylisocyanate (MDI), or polymethylene polyphenylisocyanate is a direct irritant or sensitization response. Experiments in which TDI and MDI were tested for mutagenicity and carcinogenicity are summarized. Neither chemical consistently produced positive results in the Ames test. No evidence of carcinogenicity was obtained for either compound. (33 Refs)

142. AN EVALUATION OF TESTS USING DNA REPAIR-DEFICIENT BACTERIA FOR PREDICTING GENOTOXICITY AND CARCINOGENICITY. A REPORT OF THE U. S. EPA'S GENE-TOX PROGRAM.

Leifer Z, Kada T, Mandel M, Zeiger E, Stafford R, Rosenkranz HS
Dept. Microbiology, New York Medical Coll., Valhalla, NY, 10595
Mutat Res; 87(3):211-297 1981

Methods for detection of DNA-damaging agents by repair-deficient bacterial assays are reviewed and recommendations for their improved use are made. Literature through April 1979 was searched and 91/276 papers contained analyses of 611 compounds that had been assayed in one or more of 55 pairs of repair-proficient and repair-deficient strains (38 Escherichia coli, 11 Bacillus subtilis, and 6 Proteus mirabilis). Test results and carcinogenicity data were compared in polA and other E coli, and E coli polA and B subtilis systems. In the E coli polA system, 100/269 compounds tested were positive, 35 negative and 134 gave No Test (NT) by the spot method; 24 of the latter compounds tested were also positive in the liquid assay technique. Among 45 compounds with a NT result, 23 were positive in the liquid assay and 22 were negative. When the E coli polA system was compared with other E coli strains, agreement of results was observed for 10 compounds, while 7 that were positive with polA and some of the other E coli strains were negative with WP2uvrA. A 78% correspondence between E coli polA and B subtilis rec assays was observed. Of 71 carcinogens assayed by the polA system, 44 were positive, 10 negative, and 17 gave NT or doubtful results. Of 56 carcinogens assayed with B subtilis, 21 were positive, 9 negative and 26 were NT or doubtful. One noncarcinogen tested in each assay was positive. Of the seven carcinogens assayed in P mirabilis, six were positive. E coli detected the highest percentage of alkyl epoxides and hydroxylamines; B subtilis rec the highest percentage of nitrosamines and sulfur and nitrogen oxides. Advantages and disadvantages of DNA repair assays in bacteria are listed. (98 Refs)

143. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

Genetic toxicity of epichlorhydrin (ECH) is reviewed. ECH produces gene mutations in various submammalian species, in mice, cultured mouse lymphoma cells, and in a Syrian hamster transplacental mutagenicity assay. Chromosomal damage has been reported in Vicia faba, human peripheral lymphocytes in vitro, rodent bone marrow, germ cells of mice, and in human peripheral lymphocytes and body fluids. ECH produces repairable DNA damage characteristic of an alkylating agent. The International Collaborative Program on Short-term Tests for Carcinogenicity reported that ECH was mutagenic in the in vitro systems, did not induce sex-linked recessive lethal mutations in Drosophila, and induced sister-chromatid exchanges in mammals. Application of ECH to the skin of rats and mice failed to produce tumors. Administration of ECH sc and im (but not ip) to mice produced local sarcomas and adenomas, although results were inconclusive in one study. Inhalation of 100 ppm (but not 10 ppm) of ECH for 30 days in rats induced squamous cell carcinomas in the nasal cavity. Epidemiologic studies of workers exposed to ECH provided no evidence of a carcinogenic effect; no nasal tumors were observed and the increase in lung cancers found could have been attributed to heavy cigarette consumption. Suggestions for further studies are made. (84 Refs)

144. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

Toxic and carcinogenic effects of ethylene dibromide (EDB) are reviewed. Recent experimental data has reinforced the conclusion that EDB is carcinogenic in animals and that EDB should be treated as a potential occupational carcinogen in the workplace. A ceiling limit of 0.13 ppm (1.0 mg/cubic meter) over any 15 min sampling period and use of appropriate controls to reduce worker exposure are recommended. Studies have shown a high mortality rate and a statistically significant increase in incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity in rats exposed to EDB by inhalation at 20 ppm and fed the standard rat diet. Addition of disulfiram (0.05% by wt) to the diet resulted in an approx ten-fold increase in incidence of hepatocellular carcinomas over exposure to EDB alone. The increased interaction may not necessarily be restricted to disulfiram but may occur with similarly structured compounds such as Thiram, a fungicide and seed disinfectant. Epidemiologic studies of EDB in humans have been inconclusive because of small cohort size, incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects. Gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hr for all cell stages tested. (16 Refs)

145. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.

Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981

Results of Ames microbial mutation test for industrial chemicals and future problems related to the prevention of occupational cancer in the chemical industry are reviewed. The Ames test is useful in the chemical industry because it is speedy and economical. A close relationship between mutagenicity and carcinogenicity has been observed. (32 Refs) (In JPN)

146. SENSITIVITY OF VARIOUS GERM-CELL STAGES TO ENVIRONMENTAL MUTAGENS.

Lyon MF
(c/o P. H. Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):323-345 1981

Gametogenesis is reviewed with respect to the duration of the various stages and their characteristics in terms of metabolism, chromosomal condensation, and the presence or absence of repair systems. Sensitivity of germ cell stages to mutagens is tested by dominant lethal tests, induction of specific-locus mutations, and translocations. In both males and females chemicals vary in the pattern of effects. While germ cells and their precursors are susceptible to mutagenesis at all stages, including embryonic and fetal stages, sensitivity may differ from that in the adult. Some mutagens affect certain germ-cell stages preferentially. Whether postspermatogonial rather than spermatogonial stages are affected is significant for estimating hazards of environmental mutagens. When exposure is occasional rather than continuous, the genetic hazards may be eliminated by avoidance of conception for a few mo after exposure. Although little is known about effects of chemicals on oocytes, hazards to females cannot be ignored. Rapidly dividing stages of embryonic or immature gonads may be more sensitive to certain mutagens. Effects of age on nondisjunction and on mutation rates are discussed. Germ cells of older persons may be more sensitive to the induction of both mutations and nondisjunction than those of younger persons. (122 Refs)

147. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.

Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

Biochemical and pharmacological effects of beta-carbolines in animals and man are reviewed. The major mutagenic agents in the pyrolytic products of tryptophan and proteins may be gamma-carbolines. Decreased total mutagenic activity in a mixture containing charred tryptophan has been observed after removal of the beta-carbolines harman and norharman. Addition of these compounds to an S-9 supplemented Ames assay significantly increased mutagenesis. (191 Refs)

148. 2,4-DICHLOROPHENOXYACETIC ACID - A NEW ENVIRONMENTAL MUTAGEN.

Khalatkar AS, Bhargava YR
Post-Graduate Dept. Botany, Nagpur Univ. Campus, Nagpur 440 010, India
Mutat Res; 103(2):111-114 1982

The mutagenic and teratogenic potential of 2,4-dichlorophenoxyacetic acid (2,4-D) were tested on barley (Hordeum vulgare) seeds at a concentration of 100 ppm. The compound did not affect markedly seedling height, but reduced germination and seed set. Other effects on the M1 generation included increased chromosomal aberrations, increased chlorophyll chimeras, and increased aberrant pollen mother cells and sterile pollen. In the M2 generation the chlorophyll-deficient mutations albina, viridis, chlorina, tigrina, striata, alboviridis, and viridoalba occurred, with tigrina types dominant (58-61%). While the mutagenic properties of 2,4-D demonstrated are potentially useful to breeders, caution is suggested in its use as an herbicide or hormone. (15 Refs)

149. CYTOTOXICITY, MUTAGENICITY AND DNA DAMAGE BY HOECHST 33342.

Durand RE, Olive PL
Section of Radiobiology, Johns Hopkins Oncology Center, Baltimore, MD, 21205
J Histochem Cytochem; 30(2):111-116 1982

Hoechst 33342 can be used for flow microfluorimetry (FMF) analysis of the DNA content of living Chinese hamster cells, giving good resolution (coefficients of variation (CVs) approx 6%) with relatively nontoxic staining regimens. The dye is, however, a very efficient inhibitor of DNA synthesis, with a marked depression of the DNA synthetic rate for V79 cells observed at concentrations 10-fold less than those required for optimal FMF resolution. Nontoxic and minimally toxic Hoechst concentrations also resulted in demonstrable mutation, as assayed by 6-thioguanine resistance. Hoechst disappearance from cells returned to normal growth medium after staining suggests two components of binding, since about half of the total strain is rapidly removed, whereas the rest is apparently diluted only by cell division. Cells containing Hoechst 33342 die more rapidly than control cells when held at 4 C and are also more susceptible to inactivation by the ultraviolet laser beam if operated at approx greater than or equal to 100 mW power. Thus, Hoechst 33342 can provide information about the DNA content of living cells, but at the expense of minimal toxicity, moderate mutation, and significant cell cycle perturbations. (Author abstract) (12 Refs)

150. SOMATIC MUTATIONS INDUCED BY MALEIC HYDRAZIDE AND ITS POTASSIUM AND DIETHANOLAMINE SALTS IN THE TRADESCANTIA MUTATION ASSAY.

Gichner T, Veleminsky J, Pokorny V
Inst. Experimental Botany, 16000 Praha 6, Flemingoro 2, Czechoslovakia
Mutat Res; 103(3-6):289-293 1982

Maleic hydrazide (MH), and its diethanolamine and potassium salts exhibited high mutagenic activity in Tradescantia clone 4430 and clone 02 assays. All three compounds were mutagenic to clone 4430; MH was more effective at inducing mutations in influorescences that stem cuttings. Clone 4430 was markedly more sensitive to mutagens than clone 02, a finding which disagrees with previous results. (14 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.

Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.

Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.

Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.

Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
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Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
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SERIES CK19 No. 82/07

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TESTS FOR CELL TRANSFORMATION

1. SOME ASPECTS OF IN VITRO CARCINOGENESIS USING SYRIAN HAMSTER CELLS.

Umeda M, Enaka K
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-ku, Yokohama 232, Japan
Gann Monogr Cancer Res; 27:183-194 1982

Various Syrian hamster cell lots were surveyed in order to establish reliable methods for transformation in culture.

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Growth of cells which were suitable for transformation experiments was stimulated by treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). Suitable cells showed low cell density in control cultures and high cell density in TPA-treated cultures. Cells with a capacity for abundant growth were collected by centrifugation on bovine serum albumin discontinuous density gradient. Cells with high multiplication capacity could be collected in fractions at higher density and the cells that sedimented at higher density might be a good source for transformation experiments. Establishment of a cell line likely to have characteristics of contact inhibition of growth, P-TPA cell line, is reported. Of five clones obtained, clone 54 cells exhibited a response of cell growth to TPA stimulation and low cell density in the confluent culture. Clone 54 cells had characteristics similar to those of BALB/3T3 or C3H10T1/2 cells, known to have normal growth characteristics and the capacity to be transformed by carcinogenic stimuli. P-TPA clone 54 cells responded to carcinogens and formed transformed foci. Spontaneous transformation occurred in cells cultured for more than the 20th culture generation. (23 Refs)

2. NEOPLASTIC TRANSFORMATION OF HUMAN DIPLOID FIBROBLASTS TREATED WITH CHEMICAL CARCINOGENS AND CO-60 GAMMA-RAYS.

Namba M, Nishitani K, Fukushima F, Kimoto T, Utsunomiya J, Hayflick L
Dept. Pathology, Kawasaki Medical Sch., Matsushima 577, Kurashiki 701-01, Japan
Gann Monogr Cancer Res; 27:221-230 1982

Transformation of four strains of normal human fibroblasts with repeated treatment with 4-nitroquinoline 1-oxide (4NQO) and two strains with 60Co gamma-rays is reported. Single treatment with those agents had no such effect. A total of 256 experiments were conducted, 116 with 4NQO and 49 with 60Co gamma rays. The transformed cell lines had the following features; epithelial-like morphology, unlimited growth potential, abnormal karyotypes (heteroploid), increased saturation density, reduced growth inhibition by theophylline, increased lactate dehydrogenase isozyme B(H)/A(M) ratio, no large external transformation sensitive protein, elevated colony formation in soft agar, and a low serum requirement for growth. When unlimited growth and abnormal karyotypes are present, neoplastic transformation in human cells is indicated. Criteria of the morphology of transformed colonies were defined. Advantages and disadvantages of using normal human fibroblasts for transformation studies were discussed. Future considerations for the use of normal human fibroblasts for transformation studies were proposed. (21 Refs)

3. POTENCY RANKING OF CHEMICALS BASED ON ENHANCEMENT OF VIRAL TRANSFORMATION.

Casto BC
Northrop Services, Inc., Research Triangle Park, NC
Potency Ranking of Chemicals Based on Enhancement of Viral Transformation. Available from National Technical Information Service, Springfield, VA, as PB81-210080:, 41 pp., 1981.

Treating primary hamster embryo cells with various classes of chemical carcinogens and mutagens leads to enhancement of transformation by simian adenovirus SA7. It appears that carcinogenic chemicals render the individual cells more sensitive to viral transformation, thus increasing the total number of cells integrating SA7 DNA. Enhancement of viral transformation appears to be a sensitive indicator for chemical agents with the potential to damage cell DNA by either direct or indirect means and thus may be useful as a screening tool to detect these chemicals in the environment. This report summarizes and compares the results for 134 chemicals (both carcinogenic and noncarcinogenic) assayed for enhancement of SA7 transformation, chemical transformation, and induction of DNA strand breaks and DNA repair synthesis. In addition, these chemicals are ranked by lowest effective concentration in the assay for enhancement of viral transformation. (Author abstract)

4. CELL TRANSFORMATION AS A SYSTEM FOR STUDYING MECHANISMS OF CARCINOGENESIS.

Kakunaga T, Crow JD, Lo KY, Hamada H, Kirakawa T
Cell Genetics Section, Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205
Gann Monogr Cancer Res; 27:231-242 1982

Molecular evidence of mutation occurrence in a chemically-transformed cell is presented. The value and concept of an in vitro mammalian cell transformation system for studying carcinogenesis is discussed. Six subclones of BALB/3T3A31 cells which showed constant susceptibility to induced transformation through more than 50 cell generations were highly susceptible to UV irradiation (A31-1-13), intermediately sensitive (A31-1-1, A31-1-2, and A31-1-7), and resistant (A31-1-8 and A31-1-15). These cell variants were examined for the killing effects of carcinogens, transformation induction by chemical carcinogens, transformation by tumor viruses, induction of ouabain-resistance mutation, and type and amount of DNA adducts formed after treatment with chemical carcinogens and their rate of removal. The results suggest that mutations or DNA damage induced by carcinogens have nothing to do with transformation induction, or that the transformation process involves two steps: the mutational step and a step required for expression of the transformed phenotype. A procedure for isolating a recombinant DNA containing a DNA sequence complementary to a particular messenger RNA for molecular cloning is described. (38 Refs)

5. DIFFERENCES IN ANCHORAGE-DEPENDENT GROWTH AND TUMORIGENICITIES BETWEEN TRANSFORMED C3H/10T1/2 CELLS WITH MORPHOLOGIES THAT ARE OR ARE NOT REVERTED TO A NORMAL PHENOTYPE BY ASCORBIC ACID.

Benedict WF, Wheatley WL, Jones PA
Div. Hematology-Oncology, Dept. Medicine, Childrens Hosp. Los Angeles, Los Angeles, CA, 90054
Cancer Res; 42(3):1041-1045 1982

C3H/10T1/2 mouse embryo cells were transformed with 3-methylcholanthrene. Several Type III morphologically transformed cell lines were selected with morphologies that either could or could not be reverted back to normal at passage 1 by daily addition of ascorbic acid (1 or 5 ug/ml). Those transformed cell lines with morphologies that could be caused to revert to normal did not produce colonies in agarose or tumors in nude mice at early passages. Such transformed cell lines at later passages all formed colonies in agarose, but only two of eight lines produced tumors at any passage tested. Subsequently, clones of transformed cells from each cell line have been isolated which are tumorigenic. In contrast, the transformed cell lines which were unresponsive to ascorbic acid at passage 1 were able to form colonies and to produce tumors in early passages. The reversion of the transformed morphology by ascorbic acid is apparently not caused by cytotoxicity since no cell kill was observed following exposure to ascorbate in any newly transformed cell lines at the concentrations used. Thus, the use of ascorbic acid allowed morphologically transformed cell lines to be isolated which appeared to be at different stages in the progression of an initiated cell from a morphologically transformed cell to a highly tumorigenic one. These studies also suggest that low concentrations of ascorbic acid in C3H/10T1/2/CL8 cells can be effective in suppressing oncogenic progression only prior to a stage where an initiated cell achieves the capacity to grow in semisolid medium and to produce tumors in immunosuppressed animals. The importance of these cell lines for elucidating key changes required for the promotion and/or progression of cells to a tumorigenic phenotype is also presented. (Author abstract) (6 Refs)

IN VIVO TESTS FOR MUTAGENICITY

6. DOMINANT-LETHAL TEST OF 6-MERCAPTOPURINE: DEPENDENCE ON DOSAGE, DURATION AND ROUTE OF ADMINISTRATION.

Sykora I
Res. Inst. Pharmacy and Biochemistry, Branch Inst. Pardubice-Rosice, 533 51 Pardubice, Czechoslovakia
Neoplasma; 29(6):739-746 1981

A dominant-lethal test of 6-mercaptopurine (Spofa, CSSR) was carried out in male mice with four intraperitoneal, two oral, and one subcutaneous dosage level. Furthermore, the drug was administered either in single doses or repeatedly for 7 and 14 consecutive days. With all of the dosage levels as well as administration durations and routes, a genetic risk was proved at the periods of meiotic division and late premeiotic stages of spermatogenesis, manifested by increased percentages of fetal resorptions. In relationship to the total dose administered, irrespective of the route of administration, the most marked effect increasing the frequency of resorptions within the specified period of spermatogenesis was found in the groups that had received, by repeated administrations, more than 5.5 mg of 6-mercaptopurine per one male. Fertility reduction was apparent mainly after intraperitoneal injection; the differences were significant in wk 3-5 of the test. The prenidation loss figures brought no univocal information about the interrelationship between the genetic effect and the stage of spermatogenesis. (Author abstract) (14 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

7. HOST-MEDIATED MUTAGENESIS FOR DETECTION OF MUTAGENS/CARCINOGENS.

Inui N, Nishi Y
Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Nakogi 23, Hatano, Kanagawa 257, Japan
Gann Monogr Cancer Res; 27:73-84 1982

An in vivo-in vitro combination assay, host-mediated transplacental mutation assay (HTMA), has been established in which somatic cell mutations can be detected and measured quantitatively. Two genetic markers, 8-azaguanine resistance (8AGr) and 6-thioguanine resistance, were used for detection of forward mutations in fibroblasts of Syrian hamster embryos in pregnant mothers. Mutation frequencies increased linearly with increases in the dose of furylfuramide up to 100 mg/kg body wt of the mothers, when given ip or po; higher mutagenicity was observed following po administration than after ip treatment. Data obtained by HTMA on the effects of coadministration of secondary amines and nitrite, which result in formation of nitrosamines, are presented. Administration of morpholine plus sodium nitrite (500 mg/kg, each) markedly enhanced the mutagenic effect. Coadministration of aminopyrine and sodium nitrite had a more mutagenic effect on hamster embryonic cells than single administration of either compound alone. Thus, N-nitroso compounds produced in the body do cause gene mutations in embryonic tissues and organs. The induction of 8AGr mutations was studied in cultured cells from various organs of embryos of pregnant hamsters treated with benzopyrene (BP), nitrosodimethylamine (DMN), and N-nitrosoethylurea (NMU). Treatment with BP at 200 mg/kg produced more 8AGr mutations in embryonic lung cells than in kidney, liver, or brain cells. DMN (200 mg/kg) produced the highest frequency of 8AGr mutations in the embryo liver cells. After NME administration, there was marked increase in 8AGr mutations in brain cells. Detection of somatic mutations by HMTA is discussed. (45 Refs)

8. MUTAGENICITY OF 5-AZACYTIDINE AND RELATED NUCLEOSIDES IN C3H/10T1/2 CLONE 8 AND V79 CELLS.

Landolph JR, Jones PA
Cancer Res. Lab., Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Cancer Res; 42(3):817-823 1982

To determine whether 5-azacytidine (5-AzaCR)-induced transformation and/or differentiation of C3H/10T1/2 clone 8 (10T1/2) cells might have a mutational basis, we studied whether 5-AzaCR and structurally related nucleoside analogs could mutate 10T1/2 and Chinese hamster V79 cells. In an assay for mutation to ouabain resistance in 10T1/2 cells, which detects base substitution mutations but not frameshift mutations, 5-AzaCR and 6-azacytidine were not significantly mutagenic. 5-Aza-2'-deoxycytidine, 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine, 5-fluoro-2'-deoxyuridine (FUdR), 5-bromo-2'-deoxyuridine (BUdR), and 1-beta-D-arabinofuranosylcytosine (ara-C) were only weakly mutagenic. In an assay for mutation to ouabain resistance in V79 cells, which also detects base substitution mutations but not frameshift mutations, 5-AzaCR, 5-aza-2'-deoxycytidine, FUdR, and ara-C were not detectably mutagenic, and BUdR was moderately mutagenic at highly cytotoxic concentrations. In an assay for mutation to 8-azaguanine resistance in V79 cells, which detects base substitution and frameshift mutations, 5-fluoro-2'-deoxycytidine and ara-C were weakly mutagenic, BUdR was moderately mutagenic at very cytotoxic concentrations, and 5-AzaCR, 5-aza-2'-deoxycytidine FUdR, 6-azacytidine, and 5,6-dihydro-5-azacytidine were not significantly mutagenic. Therefore, 5-AzaCR and related cytosine analogs can be considered as negligibly mutagenic. This study does not provide support for a mutational basis for 5-AzaCR-induced differentiation in 10T1/2 cells. Further, there was no correlation between the mutagenicity of the nucleosides 5-AzaCR, ara-C, BUdR, and FUdR studied here and their previously reported abilities to transform 10T1/2 cells. The mutagenicities of 5-AzaCR and FUdR were so low that the biological significance of these effects is uncertain. Hence, it is not clear to what extent, if any, mutation contributes to the transformation caused by these two compounds, and other possible mechanisms of transformation should also be investigated. (Author abstract) (49 Refs)

9. INDUCTION OF 6-THIOGUANINE-RESISTANT MUTATIONS BY RAT-LIVER HOMOGENATE (S9)-ACTIVATED PROMUTAGENS IN HUMAN EMBRYONIC SKIN FIBROBLASTS.

Chen DJ, Okinaka RT, Strniste GF, Barnhart BJ

Genetic Group, LS-3, MS886, Los Alamos Natl. Lab., Los Alamos, NM, 87545

Mutat Res; 101(1):87-98 1982

A quantitative mutation assay consisting of early passage of cultured human fibroblasts together with an exogenous rat-liver microsomal preparation to activate promutagens capable of inducing cytotoxic and mutagenic responses is described. Optimal conditions for a 6-thioguanine (6-TG) resistance mutation assay in the diploid human embryonic skin fibroblast strain (GM10) were investigated. The promutagens used were benzo[a]pyrene (BaP), 3-methylcholanthrene (3MC), and dimethylnitrosamine (DMN). At a constant amount of S9 protein concentration, a linear correlation between mutagenicity and dose was observed. At 50% survival, the mutation frequencies of BaP and 3MC 3MC (5 ug/ml) were 60 and 30x the background frequency, respectively, and DMN (5 mg/ml) induced 6-TG mutant frequencies 25x more than background. 3MC and BaP (5 ug/ml) decreased the colony-forming ability of GM10 to 50 and 20%, respectively; DMN at concentrations of 1 and 5 mg/ml inhibited colony-forming ability between 20 and 60%. At high S9 concentrations, a deactivation or detoxification phenomenon was observed. When the mutagenic efficiency of S9-activated chemicals was plotted as the number of induced mutations vs log survival it was not affected by the deactivation capacity of S9 proteins. (42 Refs)

10. THE MUTAGENIC POTENCY OF 1,8-DINITROPYRENE IN CULTURED MOUSE LYMPHOMA CELLS.

Cole J, Arlett CF, Lowe J, Bridges BA

MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England

Mutat Res; 93(1):213-220 1982

The mutagenic potency of 1,8-dinitropyrene (1,8-DNP) was compared with that of 4-nitroquinoline-1-oxide (4NQO) in cultured mouse lymphoma cells. L5178Y cells were grown in suspension culture and cloned in semisolid medium. 1,8-DNP and 4NQO were dissolved in dimethylsulfoxide (DMSO). DMSO alone had no effect on growth, cloning efficiency, or mutation frequency. Mutagenicity of test compounds was measured as the frequency of induction of resistance to 6-thioguanine (TG), methotrexate (MTX), ouabain (OUA), or 1-beta-D-arabinofuranosyl cytosine (ARA-C). Max mutation frequencies were obtained with 48-96-hr exposures for OUA, ARA-C, and MTX and with 144-192-hr exposures for TG. 1,8-DNP was not toxic at concentrations up to the max 2.5 ug/ml. Both 1,8-DNP and 4NQO produced dose-dependent increases in mutation frequencies in all mutation systems. Mutations evidently occurred by base-pair substitutions. Since previous studies had shown that 1,8-DNP produces frame-shift mutations in Salmonella and Escherichia coli, results suggest that 1,8-DNP produces mutations by different mechanisms in bacteria and mammalian cells. Problems of comparing mutagenicity of test chemicals when concentrations, treatment times, and toxicity are significantly different are discussed. (20 Refs)

11. THE INDUCTION OF MUTATION AND CELL DIFFERENTIATION BY CHEMICALS WHICH INITIATE OR PROMOTE TUMOR FORMATION.

Huberman E

Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439

Gann Monogr Cancer Res; 27:127-144 1982

Detection of tumor promoting chemicals in mammalian cell culture systems is described. Chemical carcinogens are mutagenic for mammalian cells, with their degree of mutagenicity correlating with their degree of carcinogenicity. In some cases, the metabolites responsible for mutagenesis are also responsible for initiating the carcinogenic event. A cell/organ type specificity can be established with a cell-mediated assay. The effect of tumor promoters such as the phorbol-diesters in cultured human HO melanoma and human HL-60 promyelocytic leukemia cells was studied. In both HO and HL-60 cells, the ability of ten different phorbol esters to induce differentiation correlated with their tumor-promoting activity in mouse skin. Changes in polyamine levels may involve biological pathways other than the known biosynthetic ones and these pathways or their by-products may be involved in the control of cell growth and differentiation in HL-60 cells. Studies of specific binding of 20-[3H]-phorbol 12,13-dibutyrate (PDBu) in HL-60 cells demonstrated that down regulation of specific PDBu binding is an important phenomenon involved in the mechanism of action of phorbol esters and may lead to modification of various biological and biochemical events involved in cellular differentiation and perhaps tumor promotion. Human HO melanoma and HL-60 leukemia cells may be useful for studying the mode of action of known tumor promoters and in the identification of some unknown classes of tumor-promoting agents. (82 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

12. EPIDEMIOLOGIC STUDIES OF MUTAGENICITY OF BREAST FLUIDS - RELEVANCE TO BREAST CANCER RISK.

Petrakis NL, Pike MC, Korenman SG

Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143

Banbury Rep; 8:243-255 1981

Secretion and accumulation of certain chemical substances by the breast might result in initiation and promotion of benign and malignant breast disease. Breast fluid collected from 456 women was tested for mutagenic activity with the Ames Salmonella mutagenicity test. Putative mutagenic substances were present in the breast fluids of 6.7% of the women. High concentrations of hormones have been found in breast aspirates which could act as promoting factors. Preliminary data on cerumen type and cytologic dysplasia suggested that a genetic factor affecting breast secretion may indirectly influence exposure of breast epithelia to carcinogens. (32 Refs)

13. COMPARATIVE MISONIDAZOLE METABOLISM IN ANAEROBIC BACTERIA AND HYPOXIC CHINESE HAMSTER LUNG FIBROBLAST (V-79-473) CELLS.

Koch RL, Rose C, Rich TA, Goldman P
(c/o Goldman) Div. Clinical Pharmacology, Beth Israel Hosp., Boston, MA, 02215
Biochem Pharmacol; 31(3):411-414 1982

The metabolism of the radiation sensitizer misonidazole was similar in anaerobic cecal contents and hypoxic Chinese hamster lung fibroblasts (V-79-473). Both systems formed the amino derivative of misonidazole, [1-(2-aminoimidazol-1-yl)-3-methoxypropan-2-ol] (AIM), and urea, as well as a metabolite, (2-hydroxy-3-methoxypropyl)-guanidine (G), which has not been described previously. It appears that the nitro group of misonidazole was reduced to form AIM and that this compound was then hydrolyzed to yield either urea or G, the latter in yields of 25% (tissue culture) to 55% (cecal contents). When tested with the Ames tester strain, both G and AIM were slightly mutagenic only for strain TA 98 and then only in the presence of the system for microsomal activation. (Author abstract) (11 Refs)

14. CORRELATION BETWEEN THE ASSOCIATION AND THE DESMUTAGENICITY OF BENZO(A)PYRENE BY HEMIN: COMPARISON WITH HEMOPROTEINS, TRANSIENT METALS AND AMINES.

Yagi M, Akagawa S
Dept. General Education (Physics Lab.), Tokyo Medical and Dental Univ., Ichikawa, Chiba, 272, Japan
Cancer Biochem Biophys; 5(3):175-181 1981

Benzo(a)pyrene (BP) binding was accomplished in methanol:H20 (3:1) for 10 min on thin-layer chromatography plates with the following compounds: beef hemin, beef methemoglobin, human oxyhemoglobin, beef liver catalase, p-phenylenediamine (pPDA), hydroxylamine, 3,3'-diaminodipropylamine (DADPA), cupric chloride, and ferric chloride. After binding, unbound BP was removed and its concentration determined by fluorescence in dimethyl sulfoxide soln. Association constants (Kass) of BP with hemin and other compounds were determined by an equation relating the difference between free and bound fluorescence intensities. Mutation assay was by a modified Ames method with Salmonella typhimurium strain TA100; a desmutagenicity constant (Kmut) was calculated by a similar difference method. The loss of mutagenicity of BP was caused by binding with materials containing ferric but not ferrous iron. Kass and Kmut were, respectively, 8.5 x 10(4) and 7.0 x 10(4) for hemin and 2.2 x 10(3) and 2.3 x 10(3) for DADPA. The respective figures for other compounds were both less than 1,000 (FeCL3, pPDA) or differed by a large amount (CuCl2, hydroxylamine). (20 Refs)

15. RETINOL (VITAMIN A) AS A MODIFIER OF 2-AMINOFLUORENE AND 2-ACETYL-AMINOFLUORENE MUTAGENESIS IN THE SALMONELLA/MICROSOME ASSAY.

Busk L, Ahlborg UG
Toxicology Lab., Natl. Food Admin., Box 622, S-751 26 Uppsala, Sweden
Arch Toxicol; 49(2):169-174 1982

Vitamin A (retinol) has been demonstrated to modify the mutagenic activity of the aromatic amines, 2-aminofluorene (2AF) and 2-acetylaminofluorene (2AAF) when added to the Ames Salmonella/mammalian microsome assay. Low amounts of retinol (2-20 ug/plate) increased the mutagenicity of both 2AF and 2AAF. At higher doses (50-150 ug/plates) the mutagenicity of 2AAF remained unchanged while the mutagenicity of 2AF gradually decreased. The present data do not support the hypothesis that retinol generally acts as an inhibitor of in vitro metabolic activation of procarcinogens. (Author abstract) (16 Refs)

16. MUTAGENICITY OF AZO DYES IN THE SALMONELLA/ACTIVATION TEST.

Robertson JA, Harris WJ, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Carcinogenesis; 3(1):21-25 1982

The detection of certain bis-azo biphenyl dyes (Trypan blue, Evans blue and Congo red) by a modification of the standard Ames test protocol is reported. Detection of a mutagenic response required both the inclusion of FMN in S-9 mix and use of a static pre-incubation step prior to addition of top- agar and pouring in the usual manner. Evidence is presented to substantiate the proposal that use of this protocol provides optimal conditions for the two stages of activation required for the production of mutagenic metabolites from these dyes. These are (i) initial flavin-mediated (hepatic) azo reduction resulting in the formation of proximate mutagenic metabolites followed by (ii) the oxidative metabolism by S-9 resulting in the formation of ultimately mutagenic products. (Author abstract) (16 Refs)

17. EVALUATION OF COAL LIQUEFACTION TECHNOLOGIES BY SALMONELLA MUTAGENESIS.

Warshawsky D, Shoeny R, Moore G
Dept. Environmental Health, Kettering Lab., 3223 Eden Ave., Cincinnati, OH, 45267
Toxicol Lett; 10(2/3):121-127 1982

Selected coal liquefaction materials were evaluated for mutagenicity in the Salmonella/microsome assay. Light oil products were found to be weakly or nonmutagenic. Heavy oils, such as vacuum bottoms, produced the greatest mutagenic activity. The separator bottoms and the filtered liquids produced intermediate mutagenic effects. Overall, none of the samples were found to be directly mutagenic for any Salmonella strain in the absence of rat liver homogenate. Variables influencing the relative mutagenicity of the fractions included ash content, temperature of the reactor, amount of hydrogen used, and pressure used in the vacuum distillation of the separator bottoms. (14 Refs)

18. MUTAGENS IN EXTRACTS OF GASTROINTESTINAL MUCOSA.

Stemmermann GN, Mower H, Rice S, Ichinotsubo D, Tomiyasu L, Hayashi T, Nomura A, Mandel M
Pathology Dept., Kuakini Medical Center, Honolulu, HI, 96817
Banbury Rep; 7:175-183 1981

Mucosal specimens from 60 resected stomachs (31 from stomach cancer patients) and 25 colons (11 from colon cancer patients) were assayed for the presence of mutagenic compounds in Salmonella typhimurium TA98 and TA100. The specimens for assay were not grossly involved with cancer. Nitrosated TA98 mutagens were identified in 32/60 stomach specimens, mostly from the antrum. Both sex and age seemed to play a role in determining whether the antral tissues contained mutagens. The TA98 mutagens derived from the antral mucosa were generally nitrosated derivatives of diazepam, hydroxyzine, and cimetidine (which had been used in anesthesia), which does not mean that these agents are carcinogenic in the stomach or any other organ. However, their presence in the stomach serves as a model for the in vivo generation of nitrosated mutagenic compounds. The metabolic process can occur in the absence of dietary nitrite, provided that the gastric epithelium is exposed to any one of a wide variety of amide precursors. These observations support the epidemiologic findings of an inverse correlation between stomach cancer and the intake of foods containing substances (eg, ascorbic acid and vitamin E) blocking the nitrosation process. The intestinal specimens yielded a wide variety of TA98 and TA100 mutagens, which were not characterized chemically. Some of these mutagens seemed to favor specific sites in the colon. (6 Refs)

19. NITROSATION REACTIONS OF STOMACH MUCOSAL TISSUE OF THE HUMAN AND DOG.

Rice S, Ichinotsubo D, Stemmerman G, Hayashi T, Palumbo N, Sylvester S, Nomura A, Mower H, Goldman P, Mower HF, Tannenbaum SR, Goldin BR, Fine DH, Hill MJ, Reddy BS, Hecht SS, Newmark H
Dept. Chemistry, Univ. Hawaii, Honolulu, HI, 96817
Banbury Rep; 7:185-203 1981

Gastric mucosa specimens from patients who had received hydroxyzine-HCl (HZ), diazepam (DP) and cimetidine before gastrectomy, were assayed for mutagens in Salmonella strains TA98, TA100, TA1535, and TA1537. Mutagenic activity was identified in 21/65 specimens. High pressure liquid chromatographic assays identified the mutagens as nitrosated metabolites of HZ and DP. The enzymes required to metabolize these agents were never found simultaneously in the same specimen. The antral mucosa seemed to be unique among human gastrointestinal tissues in its ability to produce nitrosated metabolites of HZ and DP. No metabolites of fenantyl were found in the human tissues. Specimens of gastric antral mucosa from dogs (without prior drug treatment) contained several mutagens, mostly of the TA98 direct-acting type, in about 20% of cases. A similar number of mutagens occurred in the lower colon mucosa. The enzymes of the canine antral mucosa were capable of nitrosating HZ, DP, and fenantyl. No mutagenic metabolites were identified when human or canine antral mucosa was incubated with cimetidine in vitro, or in the antrum of a dog treated with dinitrosocimetidine 24 hr previously, but chemically synthesized nitrosated analogs of cimetidine showed mutagenic activity in all Salmonella strains except TA98. No component of the diet or environment is known to be nitrosated by the enzyme system discovered in the human antral mucosa, but the experiments with canine tissues suggested that some dietary or environmental components probably do interact with the nitrosative metabolism of the gastric or colonic mucosa. (4 Refs)

20. THE USE OF BACTERIAL FLUCTUATION TESTS IN STUDIES OF MUTAGENIC ACTIVITY IN HUMAN FECES.

Venitt S, Pickering SP, Hill MJ, Fernandez F
Pollards Wood Res. Station, Chester Beatty Res. Inst., Inst. Cancer Res.: Royal Cancer Hosp., Chalfont St. Giles, Bucks, HP8 4SP, England
Banbury Rep; 7:239-245 1981

Fecal excretion of mutagenic substances was identified in 4/7 normal subjects with Salmonella typhimurium TA100 and Escherichia coli WP2uvrA(p) (a tryptophan-requiring strain). Metabolic activation was not required. High doses of the substances were toxic to the bacteria. The bacterial fluctuation test (method of Gatehouse and Delow) showed a significant dose-response relationship was present in each assay. This assay method can be used with any genetic system involving mutation for auxotrophy to nonleaky prototrophy. (8 Refs)

21. RELATIONSHIP BETWEEN FLUORESCENCE OF POLYNUCLEAR AROMATIC HYDROCARBONS IN COMPLEX ENVIRONMENTAL MIXTURES AND SAMPLE MUTAGENICITY.

Litten S, Babish JG, Pastel M, Werner MB, Johnson B

Toxic Substances Control Unit, Div. Water, New York State Dept. Environmental Conservation, Albany, NY, 12233

Bull Environ Contam Toxicol; 28(2):141-148 1982

The relationship between polynuclear aromatic hydrocarbon fluorescence on thin layer chromatography plates and mutagenicity assays was studied in extracts of 92 samples from sites in New York State. Samples included sewage plant sludges, industrially and non-industrially affected soils and sediments, material from landfills, and biological samples from a variety of urban and rural settings. About 30 g (4 g for biological samples) were extracted with a mixture of dichloromethane and acetone (4:1). Mutagenicity assays were performed with Salmonella typhimurium strains TA98 and TA100. A positive response was defined as a two-fold or greater increase in revertants, ie, a mutagenic index (MI) of 2 or more. Compounds with an MI less than 2 were considered nonmutagenic. Overall, 49% of the 92 samples exhibited fluorescence, and 51% mutagenicity. There was generally a good correlation between fluorescence and mutagenicity in the different types of samples, both being highest in industrially affected samples. The eight biological samples exhibited no fluorescence and two were mutagenic. Significant associations were found between fluorescence and mutagenicity for TA98 with and without activation and for TA100 with activation. A study of the overall association of fluorescence and mutagenicity in the various tests indicates that samples demonstrating fluorescence were over 5x as likely to be mutagenic than nonfluorescent samples. (15 Refs)

22. FECAL MUTAGENS IN TWO JAPANESE POPULATIONS WITH DIFFERENT COLON CANCER RISKS.

Mower HF, Ichinotsubo D, Wang LW, Mandel M, Stemmermann G, Nomura A, Heilbrun L, Kamiyama S, Shimada A

Dept. Biochemistry and Biophysics, John A. Burns Sch. Medicine, Univ. Hawaii at Manoa, Honolulu, HI, 96822

Cancer Res; 42(3):1164-1169 1982

Human feces from 223 Japanese in Hawaii at high risk for colon cancer and feces from 166 Japanese of northern rural Japan at low risk for colon cancer were shown to contain mutagenic activity under five different test conditions. The first assay, using the Ames TA98 and TA100 Salmonella test, detected ether-soluble mutagens in the presence and absence of rat liver microsomes. Of these, the TA98 direct-acting mutagens are present more frequently in the feces of the high-risk population than the low-risk population at a high level of statistical significance (p less than 0.01). TA98 mutagens activated by rat liver microsomes also occur significantly more frequently in the feces of the Japanese from Hawaii (p less than 0.05). Mutagens detected by TA100 in the presence and absence of rat liver microsomes are not commonly found in either Japanese population. The second bacterial test system used to detect fecal mutagens uses Escherichia coli rec-. This system detects water-soluble fecal mutagens which are also present more frequently in the high-risk population than in the low-risk population (p less than 0.05). (Author abstract) (27 Refs)

23. COMPARATIVE MUTABILITY OF THE AMES TESTER STRAINS OF SALMONELLA TYPHIMURIUM BY ULTRAVIOLET RADIATION AND BY 4-NITROQUINOLINE 1-OXIDE.

Nakano E, Ichikawa-Ryo H, Kondo S
Pias Co. Ltd., 3-21-3 Toyosaki, Oäyodo-ku, Osaka 531, Japan
Mutat Res; 93(1):35-44 1982

Relative mutability of five tester strains of Salmonella typhimurium and the kinetics of reverse mutation were studied after exposure to UV or 4-nitroquinoline 1-oxide (4NQO). Following UV irradiation, strain TA1538 was non-mutable; the other strains were mutable in the order TA100 greater than TA1535 greater than TA98 = TA1537. Following exposure to 4NQO the strains were mutable in the order TA100 greater than TA1538 greater than TA98 greater than TA1535 greater than TA1537. Mutability differences in relation to 'hot spot' base sequences and the nature of DNA damage are discussed. (18 Refs)

24. COMPARISON OF MUTAGENICITY AND CHEMICAL PROPERTIES OF N-METHYL-N'-ALKYL-N-NITROSOUREAS.

Isobe M, Yano K
Dept. Chemistry, Saitama Medical Sch., 981 Kawakado, Moroyama, Iruma-gun, Saitama 350-04, Japan
Mutat Res; 93(1):57-66 1982

Eleven N-methyl-N'-alkyl-N-nitrosoureas were tested for mutagenicity in Salmonella typhimurium strain TA1535. Mutagenicity was much greater for compounds with a cyclic N'-alkyl group than for those with a chain N'-alkyl group. The greatest mutagenicity was obtained with N-methyl-N'-cyclobutyl-N-nitrosourea. Mutagenicity was slightly correlated with decomposition rate but not with alkylating activity. Results suggest that mutagenicity is strongly related to the structure of N'-alkyl groups. (40 Refs)

25. LIGHT-INDUCED GENETIC TOXICITY OF THIMEROSAL AND BENZALKONIUM CHLORIDE IN COMMERCIAL CONTACT LENS SOLUTIONS.

Lovely TJ, Levin DE, Klekowski E
Univ. Pennsylvania, Sch. Medicine, Philadelphia, PA, 19104
Mutat Res; 101(1):11-18 1982

Genetic activity of 13 commercial contact lens soln and their 3 preservatives were investigated in both the Ames Salmonella assay and the Rosenkranz Escherichia coli DNA polymerase A- assay. None of the commercial products were mutagenic for any of the Salmonella tester strains. In the E coli assay, five products were genotoxic in the dark and their activity was enhanced by illumination. All four products containing thimerosal were active while only one containing benzalkonium chloride was genotoxic. In parallel experiments, irradiation of these compounds with visible light enhanced the genotoxicity of benzalkonium chloride and induced the genotoxicity of thimerosal. (17 Refs)

26. MUTAGENICITY TESTING, IN BACTERIAL TEST SYSTEMS, OF SOME CONSTITUENTS OF TOBACCO.

Riebe M, Westphal K, Fortnagel P
Institut fur Allgemeine Botanik, Abteilung Mikrobiologie, Universitat Hamburg, Jungiusstrasse 6, 2000 Hamburg 36, W. Germany
Mutat Res; 101(1):39-43 1982

The Escherichia coli polA/polA- assay for detection of repairable DNA alterations induced by mutagens and the Ames Salmonella typhimurium/microsome assay were used to test mutagenicity of 12 constituents of tobacco. None of the compounds were mutagenic in the Ames test. Positive results in the E coli test were found with pyrrolidine, nicotine, anatabine, myosmine, and 2,3'-dipyridyle; results for piperidine were inconclusive while nicotyrine was estimated to be an active substance in liquid assay. (9 Refs)

27. MUTAGENICITY TESTING OF CHLORINATED BIPHENYLS AND CHLORINATED DIBENZOFURANS.

Schoeny R
Dept. Environmental Health, Univ. Cincinnati Medical Center, 3223 Eden Ave., Cincinnati, OH, 45267
Mutat Res; 101(1):45-56 1982

The Salmonella typhimurium/microsome assay of Ames was used to assay four chlorinated biphenyls and five chlorinated dibenzofuran compounds. None of the polychlorinated biphenyls (PCB: 4-chlorobiphenyl, 3,4,3',4'-tetrachlorobiphenyl, 2,4,2',4'-tetrachlorobiphenyl, and 2,4,6,2',4',6'-hexachlorobiphenyl) reverted any of the Salmonella tester strains, which included three DNA target sequences. Assays incorporating hepati extracts (S9s) from rats treated with various inducing agents were also negative. Thus, S9 preparations from PCB-treated rats were not able to activate PCB components to detectably mutagenic forms in vitro. Dibenzofuran was assayed using dimethylsulfoxide as a solvent; the chlorinated derivatives were dissolved in a mixture of benzene:isooctane (1:9). Dibenzofuran, 2,9-dichlorodibenzofuran, 3,6-dichlorodibenzofuran, 2,3,7,8-tetrachlorodibenzofuran, and octachlorodibenzofuran were nonmutagenic for Salmonella strains TA98 and TA100 over a 3-log dose range with or without S9 activation. (37 Refs)

28. NITRITE-INDUCED VOLATILE FECAL MUTAGENS: SOME PRELIMINARY STUDIES.

MacDonald IA, Rao BG
Clinical Res. Centre, Dalhousie Univ., 5849 University Ave., Halifax, Nova Scotia B3H 4H7, Canada
Cancer; 49(7):1405-1408 1982

Further studies are reported on the formation of volatile mutagens from normal human feces incubated with sodium nitrite at 37 C. Volatile mutagens were detected using Ames' Salmonella t yphimurium tester strain TA1535 on petrie plates inverted over samples in sealed containers. An optimal exposure period was shown to be approx 24 hr. When plates inverted over samples were replaced periodically, mutagenicity during serial 24 hr or 48 hr periods could be measured. Mutagenicity was optimal during the second 24 hr period and the first 48 hr period with 0.6 M sodium nitrite, and in the first 24-and 48-hr period with 0.2 M sodium nitrite. Subsequent exposure periods showed decreasing mutagenicity with time. Because of the great differences in reactivity with nitrite in stools of healthy volunteers, the effect of mixing 'high reacting' samples with 'low reacting' samples were investigated. When 'low reacting' samples were mixed with 'high reacting' samples, a lower mutagenicity of the mixture was observed compared to a predicted 'av' value. Autoclaving stool samples made very little difference in nitrite-induced mutagenicity and behavior in mixing experiments. Thus, fecal mutagens arise as a spontaneous chemical process involving nitrite ions and both dietary and flora factors may be important in their production or absence. (Author abstract) (11 Refs)

29. PLASMA ALPHA-FETOPROTEIN ELEVATION AND MUTAGENICITY OF URINE AS EARLY PREDICTORS OF CARCINOGENICITY IN BENZO(A)PYRENE FED RATS.

Boyd JN, Misslbeck N, Babish JG, Campbell TC, Stoewsand GS
Dept. Food Science and Technology, Cornell Univ., New York State Agricultural Experiment Station, Geneva, NY, 14456
Drug Chem Toxicol; 4(3):197-205 1981

Weanling male Fischer rats were fed on diets containing benzo(a)pyrene (BaP) at (a) 0 or 1,000 ppm or (b) 0, 1, or 100 ppm for 11 wk on diet (a) or 8 wk on diet (b). Some of the animals' diet contained 500 ppm sodium phenobarbital (PB) for the last 5 wk (none getting 1,000 ppm BaP). Cardiac blood was obtained weekly at wk three and assayed for alpha-fetoprotein (AFP). Hepatic slices were obtained at wk six and stained for gamma-glutamyl transpeptidase (GGT) activity. Also at wk six 8-hr urine samples were taken and assayed by the Salmonella/mammalian microsomal test with S typhimurium strain T98. The AFP level was independent of all diets except for notable elevation at wk six in the 1,000 ppm BaP animals. Except for 1,000 ppm BaP animals assay for GGT was independent of other variables. The mutagenesis assay was positive only for the 1,000 ppm BaP animals at wk six with and without activation, and for the 100 ppm BaP with PB animals at wk eight with activation. The AFP and urinary mutagenesis assays were recommended as co-tests for short term carcinogenicity potential evaluation. (12 Refs)

CYTOGENETIC TESTS

30. CYTOGENETIC EFFECTS OF CIGARETTE SMOKE CONDENSATES IN VITRO AND IN VIVO.

Madle S, Korte A, Obe G
Institut fur Genetik, Freie Universitat Berlin, Arnimallee 5/7, D-1000 Berlin 33 , W. Germany
Hum Genet; 59(4):349-352 1981

Cigarette smoke condensates (CSC: 10-100ug/ml) from AB (reference mixture), Virginia, Burley, Orient, and HE (British) cigarettes were compared for the ability to induce sister-chromatid exchanges (SCE) in human lymphocytes in vitro. AB CSC (75, 150, 300 mg/kg) were tested for in vivo SCE induction in Chinese hamster bone marrow cells. SCE induction in lymphocytes was dose-dependent, and no statistical differences were found among the different CSC. By contrast, in vivo experiments showed no elevation of SCE in hamster bone marrow cells; no differences existed between male and female animals. The po administration used in the hamster experiment may have decreased the amount of CSC reaching the bone marrow cells. Experiments with Chinese hamsters cannot effectively simulate the chronic exposure experienced by humans who smoke. (41 Refs)

31. RETINOL (VITAMIN A) INHIBITS SISTER CHROMATID EXCHANGES AND CELL CYCLE DELAY INDUCED BY CYCLOPHOSPHAMIDE AND AFLATOXIN B1 IN CHINESE HAMSTER V79 CELLS.

Huang CC, Hsueh JL, Chen HH, Batt TR
Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(1):1-5 1982

Retinol (vitamin A alcohol) at the doses tested neither induced an increase of frequency of sister chromatid exchanges (SCE) nor cell cycle delay in Chinese hamster V79 cells with or without the metabolic activation of S-9 mix. However, it inhibited SCE frequencies and cell cycle delay in V79 cells induced by the indirect mutagen cyclophosphamide or aflatoxin B1. The inhibition was found to be dose and time dependent. These results suggest that retinol itself may have no direct effect on the genetic materials but rather exert its effects possibly by inhibiting the metabolic activation of an indirect mutagen or carcinogen. Thus, the antitumor activities of retinoids may not be limited to the widely accepted role of the preventing the promotion step but also the initiation step of carcinogenesis. (Author abstract) (33 Refs)

32. CHROMOSOMAL ABERRATION TESTS IN VITRO AS A PRIMARY SCREENING TOOL FOR ENVIRONMENTAL MUTAGENS AND/OR CARCINOGENS.

Ishidate M, Sofuni T, Yoshikawa K
Div. Mutagenesis, Biological Safety Res. Center, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan
Gann Monogr Cancer Res; 27:95-108 1982

Approx 500 different compounds were tested for their potential to induce chromosome aberrations in Chinese hamster lung fibroblasts in vitro and/or their mutagenic activity in Salmonella typhimurium in the Ames test. The compounds included 54 carcinogens, 97 food additives, 94 drugs for medical use, 30 pesticides, 46 natural products, and 241 miscellaneous compounds used in laboratories or industry. Overall, approx one-third of the compounds tested were positive in the chromosome test, but not all were positive in the Ames test. Approx 90% and 80% of carcinogens were positive in the chromosome test and Ames test, respectively. Carcinogens not positive in the Ames test were urethan, barbital, ethionamide, diethylstilbestrol, maleic anhydride, and 3-hydroxy anthranilic acid, thiourea, and thioacetamide. Annato, thiram, sodium erythrobate, imipramine-HCl, and vinylidene chloride were positive in the Ames test but not the chromosome test. Chemicals which induce chromosomal aberrations, particularly exchange-type aberrations at low dose levels, can be listed as warning compounds which warrant further testing by in vivo systems to predict their carcinogenic potential and/or genetic hazard in man. (16 Refs)

33. SISTER CHROMATID EXCHANGES AND MUTAGENIC CARCINOGENS.

Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Gann Monogr Cancer Res; 27:109-124 1982

Use of sister chromatid exchange (SCE) induction for detecting mutagenic effects in mammalian cells is reported. SCEs are produced with unrepaired lesions are present when the cell passed through S phase and chromosome replicated. Some chemical mutagens caused a 10-fold increase in background level of SCEs at concentrations of the chemical less than 1/100th of that required to induce ordinary chromosomal aberrations. Cultured Chinese hamster ovary cells with rat liver microsomes can be used to detect SCE induction. Suspected mutagens can be prescreened with the SCE test in sensitive mammalian cells by treating the cells in vitro with and without S-9 mix. Negative compounds should be tested in an in vivo test system to determine if the compounds can be activated under in vivo conditions. The SCE test was used to determine the following: which benzene metabolites were most likely responsible for the biologic effects, the stage of embryogenesis at which cells that are genetically capable of producing aryl hydrocarbon hydroxylase activated promutagens or procarcinogens, how long lesions induced by a short-lived proximate carcinogen last in cells of differing repair capacity, and whether mammalian cells exhibit novel DNA repair mechanisms. (58 Refs)

34. DOSE- AND TIME-RESPONSE RELATIONSHIPS OF TRIETHYLENEMELAMINE-INDUCED CHROMOSOMAL ABERRATIONS IN RAT BONE MARROW CELLS.

Levine BS, Pergament E, Driscoll K
Drug Safety Evaluation Div., Ortho Pharmaceutical Corporation, Raritan, NJ, 08869
Toxicol Lett; 10(2):281-285 1982

Variables and optimal conditions necessary for the use of triethylenemelamine (TEM) as a positive control agent in rat cytogenetic assays were studied. TEM-induced chromosome aberrations were observed 6 and 24 hr and to a significantly lesser extent 48 hr after single ip doses of 0.125 to 0.50 mg/kg. Single doses of either 0.25 or 0.50 mg/kg TEM with sampling of bone marrow cells 24 hr after treatment resulted in the greatest yield of chromosomal aberrations. Because 0.50 mg/kg may have been cytotoxic, the 0.25 mg/kg dose level and 24 hr killing apparently represent optimal conditions for using TEM as a positive control agent. (10 Refs)

35. INDUCTION OF CHROMATID BREAKAGE BY CLASTOGENS IN CELLS OF G2 PHASE.

Hsu TC, Cherry LM, Pathak S
Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Mutat Res; 93(1):185-193 1982

Clastogenicity of several compounds was tested in cultures of human peripheral blood cells in G2 phase. Cells were exposed simultaneously to Colcemid and actinomycin D (AMD: 2.8 uM for 15, 30, 45, or 60 min or 2.8, 1.4 or 0.28 uM for 60 min). Chromosome breakage was induced in a dose-dependent manner. The most frequent aberrations were chromatid breaks; chromatid exchanges were rare. In a modified procedure, cells were exposed to 2.8 uM AMD for 90 min, but to Colcemid for only the last 60 min. Among 100 metaphase figures 95% had chromatid breaks; the av number of breaks/cell was 3.77. Autoradiographic studies indicated that all chromatid aberrations occurred during G2 phase. Additional clastogens were tested at 100 uM concentrations (or at lower concentrations when 100 uM was too toxic). Chromatid breaks were produced by adriamycin, bleomycin, neutral red, gentian violet, and 1,4-dihydroxy-5,8- *[2-(2 hydroxymethyl)amino]ethylamino* -9,10-anthracenedione at 15-100x the frequency produced in controls. No increases in the frequency of chromatid breaks were produced by mitomycin C, hydroxyurea, ethidium bromide, or cytosine arabinoside. Cis-platinum II produced borderline results. N-Methyl-N'-nitrosoguanidine was mildly clastogenic in G2 phase. Results indicate that a simple protocol can be used to determine clastogenicity in G2-phase cells. (8 Refs)

36. GENETIC DAMAGE CAUSED BY METHYLAZOXYMETHANOL ACETATE, THE AGYLCONE OF CYCASIN. ANALYSIS OF SISTER-CHROMATID EXCHANGE FREQUENCY UNDER IN VIVO CONDITIONS AND IN CELL CULTURES.

Gloser H
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-109 Vienna, Austria
Oncology; 39(2):101-103 1982

To extend the information on the mutagenic effect of methylazoxymethanol (MAM) acetate, which has been established as a potent carcinogen, the frequency of sister-chromatid exchange (SCE) was determined in bone marrow cells of Sprague Dawley rats and in cultured rat lymphocytes. To get differentially stained chromatids under in vivo conditions, the rats received 5-bromodeoxyuridine adsorbed on activated charcoal intraperitoneally. Chromosomes were stained with fluorescence plus Giemsa. In this study a significant increase of SCE frequency after the application of various concentrations of MAM acetate could be observed both in vivo and in vitro. (Author abstract) (20 Refs)

37. PHARMACOKINETICS AND MACROMOLECULAR INTERACTIONS OF ETHYLENE DICHLORIDE IN RATS AFTER INHALATION OR GAVAGE.

Reitz RH, Fox TR, Ramsey JC, Quast JF, Langvardt PW, Watanabe PG
Toxicology Res. Lab., 1803 Building, Dow Chemical USA, Midland, MI, 48640
Toxicol Appl Pharmacol; 62(2):190-204 1982

Pharmacokinetics and macromolecular interactions of ethylene dichloride (EDC) were studied in male Osborne-Mendel rats after inhalation or gavage. The doses were 150 mg/kg (gavage) or 150 ppm/6 hr (inhalation), representing the highest levels of EDC administered for any significant length of time in the two bioassays. Major routes of elimination after exposure to unmarked and 14C marked EDC were studied. EDC was readily absorbed; peak blood levels occurred within 15 min following gavage and at 1-2 hr during continuous inhalation. EDC was rapidly eliminated after either administration. Urinary metabolites were thiodiacetic acid and thiodiacetic acid sulfoxide. Macromolecular binding measured shortly after exposure was diffuse. Covalent alkylation of DNA by EDC studied in Salmonella typhimurium was directly related to frequency of mutation in the bacteria. DNA purified from the organs of rats exposed in vivo showed very little alkylation; 2-20 alkylations/million nucleotides. DNA alkylation after gavage was 2-5x higher than after inhalation. Peak blood levels were approx 5x higher after gavage than after inhalation. Pharmacokinetic data indicated that elimination of EDC may become saturated when high blood levels are produced; saturation is more likely to occur when equivalent doses are administered by gavage than by inhalation. (32 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

38. THE DETECTION OF GENOTOXIC CHEMICALS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

Williams GM
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Gann Monogr Cancer Res; 27:45-55 1982

Use of the hepatocyte primary culture (HPC)/DNA repair test for detection of genotoxic chemicals is reported. Hepatocytes obtained from livers of rats, mice, hamsters, or rabbits are cultured on plastic coverslips and exposed to the test chemical for 5-18 hr with 3H-thymidine. Cells are then fixed and processed for emulsion autoradiography. Of 73 compounds tested, 96% of known carcinogens were positive, 8 chemicals of unknown carcinogenicity were positive and 2 were negative, and all 13 noncarcinogens were negative. The test can be used to examine species differences in xenobiotic biotransformation and DNA repair response in a specific, well characterized cell type. Since liver cells do not respond to chemicals requiring bacterial metabolism, supplementation with the specific bacterial enzyme suspected of being involved in the biotransformation of the test chemical may be useful. All hepatocarcinogenic drugs and organochlorine pesticides were negative in the HPC/DNA repair test, supporting the concept that these carcinogens operated by epigenetic mechanisms, which in some cases appear to be promoting effects. Use of this test with other in vitro short-term tests may be useful for classifying carcinogens as epigenetic. (39 Refs)

39. IN VITRO ALKYLATION TESTS: COMPARISON OF THE ALKYLATION RATE AND MUTAGENICITY.

Hemminke K, Falk K, Vainio H
Inst. Occupational Health Care, Helsinki, Finland
Gig Tr Prof Zabol; (1):43-44 1982

Alkylating activity of a series of epoxy-containing compounds was studied in 4-(p-nitrobenzyl)-pyridine and deoxyguanosine tests. The alkylation rate showed a correlation with the mutagenic activity. These findings indicate that simple in vitro alkylation tests can be used for the preliminary estimation of the mutagenicity. (7 Refs) (In RUS)

40. ALKYLATING PROPERTIES OF DICHLORVOS (DDVP).

Segerback D, Ehrenberg L
Dept. Radiobiology, Wallenberg Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):56-66 1981

Dichlorvos (DDVP) is a methylating agent. In DNA from mice given 1.9 x 10(-6) mol/kg of DDVP, a degree of alkylation of guanine-N-7 amounting to 8 x 10(-13) mol methyl per g DNA, was found. From this, a rate of clearance of 29 hr-1 was estimated. This value is in reasonable agreement with the value (55 hr(-1)), calculated from published data on the concentration over time of DDVP in the brain after injection of the compound in mice. Applying a risk estimation on humans exposed to DDVP, the genetic risk connected with the methylating activing of DDVP is low or very low. Comparing the mutagenic effectiveness of DDVP with that of methyl methanesulfonate, indicates that DDVP is more effective than expected from reaction kinetic data. The possible contribution of the dichloroacetaldehyde formed in vivo from DDVP has to be evaluated before a complete risk estimate can be made for DDVP. (Author abstract) (46 Refs)

41. COMPARISON BETWEEN SENSITIVITY OF A VISCOMETRIC METHOD AND SENSITIVITY OF THE ALKALINE ELUTION ASSAY FOR THE DETERMINATION OF DNA DAMAGE INDUCED BY DIMETHYLSULFATE IN VITRO.

Parodi S, Balbi C, Taningher M, Abelmoschi ML, Pala M, Parodi G, Santi L
Inst. Oncology, Genoa Univ., Genoa, Italy
Toxicol Lett; 10(4):351-358 1982

DNA damage induced by dimethylsulfate (DMS) in rat liver nuclei was assessed by a new viscometric method. Control DNA reached maximum viscosity in 8 hr. DNA treated with increasing doses of DMS reached maximum viscosity in progressively shorter times. The viscometric method is about 30 times more sensitive than the alkaline elution assay, and is one of the most sensitive methods for evaluation of alkaline DNA fragmentation in terms of DNA disentanglement. (7 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

42. STIMULATION OF S-9 FRACTION METABOLISM IN RAT LIVER AND BREAST BY VITAL DYES.

Silva MH, Lee RE, Petrakis NL
Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143
Toxicol Lett; 10(2/3):205-208 1982

Known mutagens metabolized in rat liver and breast supernatant fractions were used in the Ames test to assess metabolizing enzyme induction by vital dyes. The mutagen 2-aminoanthracene (2AA) showed a 70% activity increase with neutral red, an 89% increase with methylene blue, and a 49% increase with trypan blue in treated rat liver fractions. The lowest and greatest increase in mutagenic activity with liver fractions was seen with 6-aminochrysene and diaminofluorene, respectively. An activity increase in treated breast fractions was found only with 2AA. Liver tissue was more readily induced than mammary glands of midpregnant rats. (11 Refs)

43. INFLUENCE OF LIVER S-9 PREPARATIONS FROM RATS AND RAINBOW TROUT ON THE ACTIVITY OF FOUR MUTAGENS.

De Flora S, Zanacchi P, Bennicelli C, Arillo A
Inst. Hygiene, Sch. Medicine, Univ. Genoa, 16132 Genoa, Italy
Toxicol Lett; 10(4):345-349 1982

The effects of rat and trout liver post-mitochondrial fractions on benzo(a)pyrene (BP), 2-aminofluorene (2-AF), aflatoxin B1 (AFB1), and sodium dichromate in the Ames reversion assay were compared. Rat preparations were significantly more efficient in activating AFB1 and 2-AF. Rat and trout preparations were equally effective in decreasing the direct mutagenicity of sodium dichromate. Rat microsomes were virtually ineffective and trout preparations were slightly active in producing mutagenic metabolites from BP. (14 Refs)

44. THE EFFECTS OF DIETARY SELENIUM ON THE BIOTRANSFORMATION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Schillaci M, Martin SE, Milner JA
(c/o Martin) Dept. Food Science, Univ. Illinois, Urbana, IL, 61801
Mutat Res; 101(1):31-37 1982

Effects of dietary selenium on mutagenicity of 7,12-dimethylbenz[a]anthracene (DMBA) following incubation with liver microsomes from Sprague-Dawley rats given Se in drinking water (5 ppm) or in the diet (0.1, 2.5, or 5 ug/g) for 3 wk were investigated. All rats also received 0, 20, 50, 100 or 500 mg Aroclor 1254/kg body wt. Addition of Se to the drinking water significantly reduced final body wt of the rats and increased plasma Se. S9 liver microsome preparations from the rats did not differ in Se content. The number of revertants in the Salmonella typhimurium test increased approx 280% when the amount of Aroclor was increased from 20 to 100 mg/kg. Livers from rats induced with Aroclor (20-100 mg/kg) receiving Se had a reduced ability of S9 preparations to induce transformation of DMBA (71 and 31% reductions in the number of revertants compared with controls at the 20-and 100-mg/kg induction levels, respectively). Se supplementation of the diet significantly reduced the capability of the rat-liver fractions to transform DMBA. With 2.5 ppm Se, the number of revertants/plate decreased from 68 to 37 at the 20-mg/kg level of Aroclor induction. At 50 and 100 mg/kg induction levels, colonies/plate decreased from 159 to 18 and 136 to 41, respectively. Se at 5 ppm reduced the number of revertants/plate from 68 to 20, 154 to 51, and 136 to 47, at the 20-, 50-, and 100-mg/kg induction levels of Aroclor, respectively. Thus, in vivo Se supplementation may reduce susceptibility to various carcinogens. (24 Refs)

45. INVESTIGATION OF STYRENE IN THE LIVER PERFUSION/CELL CULTURE SYSTEM. NO INDICATION OF STYRENE-7,8-OXIDE AS THE PRINCIPAL MUTAGENIC METABOLITE PRODUCED BY THE INTACT RAT LIVER.

Beije B, Jenssen D
Div. Cellular Toxicology, Environmental Toxicology Unit, Univ. Stockholm, Wallenberg Lab., S-10691 Stockholm, Sweden
Chem Biol Interact; 39(1):57-76 1982

Mutagenic effect of styrene and styrene-7,8-oxide was studied with the isolated perfused rat liver as metabolizing system and Chinese hamster V79 cells as genetic target cells. Styrene-7,8-oxide which is mutagenic per se was rapidly metabolized by the perfused rat liver. Thus no mutagenic effect was detected either in the perfusion medium or in the bile. However when styrene was added to the perfusion system, an increase in V79 mutants was observed regardless of where in the circulating perfusion medium the V79 cells were placed: the same effect was obtained with V79 cells close to the liver as well as at a distance from the liver. No mutagenic effect was observed in the bile. Simultaneous analysis of the styrene-7,8-oxide concentration in the perfusion medium, suggest that this metabolite is not the cause of the mutagenic effect observed during perfusion with styrene. The effect of the two test compounds on some liver functions was also studied. It is suggested that the results on styrene and styrene-7,8-oxide found here using the liver perfusion/cell culture system mimic the metabolism expected to be found in the intact animal, thus indicating that styrene-7,8-oxide is not the principal mutagenic metabolite of styrene in vivo. (42 Refs)

COMPARATIVE TEST RESULTS

46. CARCINOGENIC AND MUTAGENIC ACTIVITY OF AN ALKALOIDAL EXTRACT OF SENECIO NEMORENSIS SSP FUCHSII.

Habs H, Habs M, Marquardt H, Roder E, Schmahl D, Wiedenfeld H
Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Arzneim Forsch; 32(2):144-148 1982

The alkaloidal residue obtained after extraction of dried and pulverized Senecio nemorensis ssp fuchsii contains two pyrrolizidine alkaloids, ie fuchsisenecionine and senecionine. In a chronic experiment doses of 8 mg/kg and 40 mg/kg bw of the alkaloidal extract were given 5x a wk by gavage to male and female Sprague-Dawley rats. The study was terminated after 114 wk. Repeated serum analysis demonstrated a dose-related elevation of serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (AP). Beside its hepatatoxic effect, the treatment proved to be hepatocarcinogenic, showing female rats to be more sensitive than males. Tumors diagnosed were of hepatocellular and angiogenic origin. In age-adjusted analysis the occurrence of these neoplasms revealed a clear dose-related trend (p less than 0.00005). In the in-vitro mutagenicity test system with V79 Chinese hamster cells, the alkaloidal extract exerted a weak but dose-related mutagenic activity. Under the conditions used the alkaloidal extract of Senecio nemorensis ssp fuchsii is a genotoxic carcinogen. (Author abstract) (28 Refs)

47. CELL TRANSFORMATION, MUTATION, AND CANCER.

Barrett JC
Environmental Carcinogenesis Group, Natl. Inst. Environmental Health Sciences, Lab. Pulmonary Function and Toxicology, NC, 27709
Gann Monogr Cancer Res; 27:195-206 1982

The abilities of 2-aminopurine (AP) and diethylstilbestrol (DES) to induce neoplastic transformation and/or somatic mutation in Syrian hamster embryo cell assays was investigated. AP is a well-defined mutagen and an inactive carcinogen, while DES is a known carcinogen and is inactive as a mutagen. AP was shown to be, at best, a weak transforming agent. DES failed to induce measurable somatic mutations at either of the two loci tested. At the chromosome level, a mutation is one cause of morphological transformation and possibly cancer. Chromosome changes are very early manifestations of a neoplastic alteration and may be an initial part of neoplastic development in vivo. A theory on the relationship between tumor initiation, differentiation, and chromosome mutations is proposed. The carcinogen induces chromosome mutations, gene mutations, and nonmutational changes, any of which might lead to neoplastic development. The most frequent event results from a chromosome mutation which prevents normal cellular differentiation, thereby providing a selective growth advantage for the altered cells. The altered cell grows and mutational or nonmutational secondary changes may occur. (63 Refs)

48. USE OF FOUR SHORT-TERM TESTS TO EVALUATE THE MUTAGENICITY OF MUNICIPAL WATER.

DeMarini DM, Plewa MJ, Brockman HE
(c/o Brockmann) Dept. Biological Sciences, Illinois State Univ., Normal, IL, 61761
J Toxicol Environ Health; 9(1):127-140 1982

Raw and treated water from Lake Bloomington was studied with four different mutation tests: the Salmonella/microsome test, a mitotic gene conversion test in strain D4 of Saccharomyces cerevisiae, the adenine-3 forward mutation test in Neurospora crassa, and a reverse mutation test with two alleles of the waxy locus in Zea mays. All 54 samples were not tested in each of the four tests by all protocols. Water samples were collected from February to September 1976 and June to October 1977. Lake and tap water samples collected during 1976 were toxic but not mutagenic in N crassa and were neither toxic nor genotoxic in S cerevisiae. Lake water collected in 1977 was mutagenic in one Z mays line and slightly mutagenic in S typhimurium strain TA1536 with rat liver S9 mix. Results with S typhimurium indicate that some water treatment processes may reduce the mutagenic activity in drinking water. Z mays results demonstrated that lake water mutagens exhibited allelic specificity. The use of more than one test is recommended to confirm results obtained with one test, particularly when testing drinking water which may contain low concentrations of several different mutagens. Advantages and disadvantages of each of the tests are reviewed. (18 Refs)

49. METRIFONATE AND DICHLORVOS: CYTOGENETIC INVESTIGATIONS.

Moutschen-Dahmen J, Moutschen-Dahmen M, Degraeve N
Dept. Genetics, Univ. Liege, B-4000 Liege, Belgium
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):29-39 1981

Contradictory results are found in the literature about the cytogenetical effects of dichlorvos and metrifonate in mammals whereas their chromosome breaking ability was demonstrated in plant and Drosophila cells. They were tested on both in vitro and in vivo cells for chromosome breakage. Dominant lethal mutations were also investigated in mouse as well as epidemiological studies in man. In our experiments on mouse bone marrow and testis, one acute dose was injected respectively: 10 mg/kg for dichlorvos and 100 mg/kg for metrifonate. These experiments failed to reveal any clastogenic effect in these test systems as well as in chronic treatments respectively 2 ppm/5 days a wk for 7 wk for dichlorvos and 0.5 ppm 5 days a wk for 7 wk for metrifonate. In an investigation of dominant lethal mutations, dichlorvos did not enhance the frequency of dead embryos but the frequency of pre-implantation losses was significantly increased in two specific periods of the seven investigated. In the same test, metrifonate did not produce any effect. These data are compared with those obtained with trimethylphosphate and MMS taken as positive controls. These results will serve to reevaluate the cytogenetical risks of dichlorvos and metrifonate. (Author abstract) (36 Refs)

50. MULTITECHNIQUE SCREENING OF CHICAGO MUNICIPAL SEWAGE SLUDGE FOR MUTAGENIC ACTIVITY.

Hopke PK, Plewa MJ, Johnston JB, Weaver D, Wood SG, Larson RA, Hinesly T
Inst. Environmental Studies, Univ. Illinois, Urbana, IL, 61801
Environ Sci Technol; 16(3):140-147 1982

A sample of anaerobically digested Chicago sewage sludge was subjected to a multiorganism screening procedure to detect mutagenic compounds in sludge and sludge-amended soil. The sludge doubled the number of revertent colonies of mammalian microsome-activated Salmonella typhimurium strain TA98, induced point mutations in Zea mays germ cells in an in situ test, and increased the frequency of micronuclei in Tradescantia paludosa meiotic cells. (22 Refs)

51. COMPARISONS BETWEEN CARCINOGENIC POTENCY AND MUTAGENIC POTENCY TO SALMONELLA IN A SERIES OF DERIVATIVES OF 4-DIMETHYLAMINOAZOBENZENE (DAB).

Ashby J, LeFevre PA, Styles JA, Charlesworth J, Paton D
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderly Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 93(1):67-81 1982

The carcinogenic and mutagenic potencies of 4-dimethylaminoazobenzene (DAB) and several derivatives of DAB were compared. Test compounds were 5-phenylazoindazole (5I), 6-phenylazoindazole (6I), 7-phenylazoindazole (7I), 5-phenylazobenzothiazole (5BT), 6-phenylazobenzothiazole (6BT), and 7-phenylazobenozothiazole (7BT). Reference compounds were DAB, the noncarcinogen 4'-dimethylamino-4-dimethylaminoazobenzene (Compound II), and the potent carcinogen 2'3'-dimethyl-4-dimethylaminoazobenzene (Compound III). S9 mix was prepared from livers of male Sprague-Dawley rats treated with Aroclor 1254. Mutagenicity was measure in Salmonella typhimurium strain TA98 in plate-incorporation (PI), liquid pre-incubation (LPI), and fluctuation tests. DAB, 5I, and 6BT were tested by ip injection into Alderley Park rats; liver tissue was examined 6 hr after injection. Results of the PI test were negative for DAB and positive for all other compounds. Results of the LPI test were positive for all compounds. The results of the fluctuation test were positive for DAB, 5I, 6I, 7I, 5BT, 6BT, and 7BT and negative for Compounds II and III. DAB and 6BT produced pathological changes in rat liver and affected the recovery profile of methylated bases derived from hepatic DNA of pretreated rats; 5I did not. The value of short-term in vivo assays, including the potential to identify potent mammalian carcinogens among structurally related compounds, is discussed. (45 Refs)

52. QUANTITATIVE CORRELATIONS AMONGST ALKALINE DNA FRAGMENTATION, DNA COVALENT BINDING, MUTAGENICITY IN THE AMES TEST AND CARCINOGENICITY, FOR 21 COMPOUNDS.

Parodi S, Taningher M, Boero P, Santi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Viale Benedetto XV, 10 I-16132 Genova, Italy
Mutat Res; 93(1):1-24 1982

Correlations between the carcinogenicity of 21 compounds and the alkaline DNA fragmentation, formation of DNA adducts, and Ames-test mutagenicity produced by the compounds were studied. Test compounds included 6 methylating agents, 3 ethylating agents, 5 aromatic amines, 2 polycyclic aromatic hydrocarbons, and 5 heterogeneous compounds thought to generate DNA adducts with greater steric hindrance than those produced by methylating or ethylating agents. Compounds were administered to adult mice and rats by oral and parenteral routes. The highest doses exceeded lethal levels. Parameters measured included the oncogenic potency index (OPI), covalent binding index (CBI), DNA fragmentation index (DFI), mutagenic potency index (MPI), and lethal dose index (LDI). All parameters were found to be correlated with carcinogenic potency; the correlation between CBI in vivo and carcinogenicity was 3x as great as the correlation between the MPI and carcinogenicity. CBI in vivo correlated strongly with DFI in vivo. Assay of the DFI for eight compounds indicated negative results for benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, 2-acetylaminofluorene, and urethane; positive results were obtained for methyl methanesulfonate, aniline, 2-naphthylamine, and benzidine. Results indicate that carcinogenic potential should be predictable from the results of a battery of appropriate tests. (28 Refs)

53. CORRELATION OF ALKYLATING AND MUTAGENIC ACTIVITIES OF ALLYL AND ALLYLIC COMPOUNDS: STANDARD ALKYLATION TEST VS. KINETIC INVESTIGATION.

Eder E, Neudecker T, Lutz D, Henschler D
Inst. Toxicology, Univ. Wurzburg, D-8700 Wurzburg, W. Germany
Chem Biol Interact; 38(3):303-315 1982

Thirty-nine allylic and non-allylic compounds have been tested in the standard 4-(p-nitrobenzyl)pyridine (NBP) alkylating procedure and the Salmonella typhimurium mutagenicity assay. Fourteen of these were found directly mutagenic (without addition of S-9 mix activating enzyme system). With 12 of these compounds, a good correlation of alkylating and mutagenic potencies was established; the remaining 2 do not meet the chemical conditions of the NBP procedure on account of HCL elimination with these 2 compounds. The other 25 substances were inactive in both systems. The quantitative correlation proved to be almost linear in the lower activity ranges (E approx 2; revertants/umol approx 600). The reasons for some deviations from the linear relationship have been analyzed and discussed on the basis of structural features. In addition to the standard alkylation test, a modified NBP-test was performed in order to obtain kinetic data and activation energy values. The results with six representative allylic compounds show that the overall correlation is not substantially improved above that of the standard procedure; nonetheless, additional information on reaction characteristics is obtained with some substances. (Author abstract) (26 Refs)

REVIEWS AND OTHER RELATED STUDIES

54. ARSENIC-STATE OF THE ART.

Landrigan PJ
Div. Surveillance, Hazard Evaluations, and Field Studies, NIOSH, 4676 Columbia Parkway, Cincinnati, OH, 45226
Am J Ind Med; 2(1):5-14 1981

Occupational and domestic exposure to arsenic in United States of America is briefly reviewed: human elimination mechanisms; assay implications; acute poisoning; subacute and chronic toxicity to the skin (dermatitis, Bowen's disease, basal cell and squamous cell carcinomas), liver (cirrhosis, angiosarcoma), respiratory tract (lung cancer), and nervous (peripheral neuropathy), cardiovascular (acrocyanosis), 'blackfoot disease' (gangrene), myocardial infarction, Reynaud's (phenomenon), and hematopoietic (disturbed erythropoiesis, equivocal cancer) systems. Animal cancer-induction studies remain negative. Mutagenicity/chromosomal aberration studies in bacterial-animal-human systems are touched upon. (50 Refs)

55. EVALUATION OF RELATIVE ENVIRONMENTAL HAZARDS FROM A COAL GASIFIER.

Gangwal SK, Cleland JG, Truesdale RS
Research Triangle Inst., Research Triangle Park, NC
Evaluation of Relative Environmental Hazards from a Coal Gasifier. Available from National Technical Information Service, Springfield, VA, as PB81-217648:, 108 pp., 1981.

The report gives results of an evaluation of relative environmental hazards from a laboratory-scale coal gasifier. Detailed chemical analyses of four effluent streams (gas, aqueous condensate, tar, and ash) were performed for more than 30 gasification runs on a variety of coals, from lignite to bituminous. It briefly describes the gasification reactor, the associated sampling and analysis system, problems encountered with analyses, and special techniques for analyzing complex samples. Relative environmental hazards were determined using the Multimedia Environmental Goals methodology. Toxicity and mutagenicity were assessed using bioassay data. More than 400 effluent stream constituents were identified. Environmentally, the most significant effluent stream is aqueous condensate, followed by tar, product gas, and ash. However, on an equivalent weight basis, the tar stream is more toxic and mutagenic than aqueous condensate. Polycyclic aromatic hydrocarbons and organic bases are the most mutagenic fractions of the tar. Coal pyrolysis and gasification at higher temperatures leads to reduced tar mutagenicity. The most environmentally significant constituents (by stream) are: (1) product gas-CO, benzene, H2S, and carbonyl sulfide; (2) aqueous condensate - phenol/cresols/xylenols (PCX), NH3, sulfides, thiocyanates, CN, As, and chlorides; and (3) ash - As, Ni, Be and Se. (Author abstract)

56. INITIATION AND PROMOTION, MUTAGENESIS AND TRANSFORMATION OF C3H/10T1/2 MOUSE EMBRYO FIBROBLASTS.

Heidelberger C
Univ. Southern California Sch. Medicine, Los Angeles, CA, 90031
Gann Monogr Cancer Res; 27:207-219 1982

The C3H/10T1/2 mouse embryo fibroblast cloned cell line is discussed with respect to initiation and promotion, mutagenesis, and transformation. Transformation by polycyclic aromatic hydrocarbons was dose-dependent and did not involve activation of an endogenous retrovirus or its cores or RNA. Metabolism of benzo[a]pyrene in microsomes of these cells involves formation of 7,8-and 9,10-diols, phenols and quinones. UV light is a pure initiator, x-rays initiate transformation, and saccharin is a weak promoter. While 12-O-tetradecanoyl phorbol-13-acetate (TPA) is strongly mitogenic and produces hyperplasia in mouse skin, it does not significantly increase the saturation density of C3H/10T1/2 cells. All chemical classes of tumor promoters are not suitable for screening by measuring their effects on the 5-azacytidine-induced differentiation of C3H/10T1/2 cells because of inconsistencies in results. Mutagenic and oncogenic transformation in these cells is described. Mutagenesis data can be interpreted in various ways in order to obtain the desired result. In this system mutagenesis appears to be necessary but is not sufficient for transformation. (60 Refs)

57. GASTROINTESTINAL CANCER: ENDOGENOUS FACTORS.

Bruce WR, Correa P, Lipkin M, Tannenbaum SR, Wilkins TD
Ontario Cancer Inst., Toronto, M4X 1K9, Canada
Banbury Rep 7: 468 pp., 1981.

The role of diet in cancer was examined. Sessions on gastrointestinal microbiology (microbiological considerations in experimental studies, effect of diet on human fecal flora, metabolism of xenobiotics by intestinal flora, and intestinal bacterial activity and carcinogenesis), fiber (ecology of gut fermentation in man, dietary fiber breakdown in the human colon role of fat, fiber, and other modifiers of intestinal carcinogenesis in cancer prevention), host response to carcinogens (risk factor profiles for individuals at increased risk for colon cancer, fecal mutagens and colorectal polyps, enzymes of normal, premalignant, and malignant colonic cells, role of cytochrome P-450 in colon response xenobiotics, inhibitors of gastrointestinal neoplasia, colonic activation of carcinogens), mutagens (in extracts of gastrointestinal mucosa, nitrosation in stomach mucosal tissue of humans and dogs, isolation of mutagens produced in the human colon by bacterial action, structural studies and properties of mutagens isolated from human feces, bacterial fluctuation tests of mutagenic activity in human feces, intake, formation, and release of mutagens by man), N-nitroso compounds (endogenous formation of N-nitroso compounds, analysis of human biological specimens for nitrosamines, block nitrosamine formation using ascorbic acid and alpha-tocopherol, distribution and metabolism of nitrate and nitrite in rats, analysis of nitrate, nitrite, and nit rosamines in human feces, metabolism of nitrate), bile acids and other lipids (bile salts as tumor promoters, bile acids in colorectal carcinogenesis, and analysis of feces for benzopyrene after consumption of charcoal-broiled beef) and epidemiology and design of future studies (epidemiologic tests of hypothesis relating diet and cancer, large-scale cohort study of diet and selected digestive system cancers, and possible application of mutagenesis testing to cancer epidemiology). (716 Refs)

58. THE METABOLISM OF XENOBIOTICS BY THE INTESTINAL FLORA.

Goldman P
Div. Clinical Pharmacology, Harvard Medical Sch., Beth Israel Hosp., Boston, MA, 02215
Banbury Rep; 7:25-39 1981

In general, the metabolism of xenobiotics involves oxidation and conjugation in the liver, with reducing and deconjugating reactions mediated by the intestinal flora. Several major metabolic reactions have been identified as carried out by the intestinal flora of rodents, but major species differences present a serious obstacle to the use of animal data to clarify the role of the intestinal flora in human colon cancer. The correlation between colon cancer and protein intake is supported by the low reported incidence of colon cancer in vegetarians; but the spouses of colon cancer patients are not at an increased risk of the disease. A susceptibility factor (familial polyposis, ulcerative colitis, etc) may be required before an effect of diet can be discerned. There is experimental evidence that the intestinal flora is essentially fixed for life by contacts during the neonatal period. This suggests that dietary alterations in later life may have little effect on the bacterial composition of an individual's intestinal flora. The differences between the compositions of the fecal flora of residents of countries with different colon cancer incidence rates can be explained in many ways, but they are at least compatible with the concept of a 'national flora' determined by a 'national diet'. It is suggested that studies on possible differences in the metabolism of xenobiotics by persons at different risks of colon cancer might give significant results if the tests involved assays of fecal mutagens rather than the microbial compositions of the intestinal flora. (50 Refs)

59. POSSIBLE APPLICATIONS OF MUTAGENESIS TESTING IN CANCER EPIDEMIOLOGY.

Haenszel W, Magee PN, Tannenbaum SR, Correa P, Hill MJ, Reddy BS, Stemmermann GN, Bruce WR, Lipkin M, Nigro ND, Venitt S, Goldin BR, Hirayama T, Archer MC, Balis ME, Keefer LK, Goldman P, Balish E, Strobel HW, Eisenbrand G
Biometry-Epidemiology Program, Univ. Illinois, Sch. Public Health, Chicago, IL, 60616
Banbury Rep; 7:431-446 1981

Epidemiological applications of mutagenesis studies for stomach and large bowel cancer are reviewed. A cohort study of stomach cancer in a high-risk population in Colombia has been proposed; positive tests for mutagenicity in gastric juice samples were found only when nitrites were present. High-risk North American populations are suitable for bowel cancer studies. Linkage of pathology, fecal chemistry, and mutagenesis data will improve screening for large-bowel cancer and help to elucidate the pathways leading to large-bowel cancer. (20 Refs)

60. USE OF PROGNOSTIC MUTAGENICITY TESTS FOR THE ESTIMATION OF LONG-TERM TOXIC EFFECTS OF CHEMICAL SUBSTANCES.

Sorsa M
Inst. Occupational Health Care, Helsinki, Finland
Gig Tr Prof Zabol; (1):39-41 1982

The efficacy of short-term mutagenicity tests for the prognosis of long-term carcinogenicity is reviewed. It was emphasized that the preliminary estimation of the carcinogenicity should be based on the results of a group of express-tests which are able to to detect gene mutations, chromosome aberrations, and primary DNA damage. (3 Refs) (In RUS)

61. ANALYSES FOR BINOMIAL DATA, WITH APPLICATION TO THE FLUCTUATION TEST FOR MUTAGENICITY.

Collings BJ, Margolin BH, Oehlert GW
Dept. Mathematical Sciences, Montana State Univ., Bozeman, MT, 59717
Biometrics; 37(4):775-794 1981

The fluctuation test proposed by Green, Muriel and Bridges, a short-term microbial test for mutagenicity, yields binomial observations for which the probability of success varies with the background mutation rate, the total number of microbial growth cycles for which a microbe is at risk of mutation, and the rate of induced mutation for the compound being tested. A standard one-tailed two-sample bionomial test is preferable to the two-tailed test adopted by Green et al for analyzing data from a control vs single positive dose fluctuation test. Based on exact power computations, recommendations are offered for the design of such a fluctuation test. A simple method of guarding against the impact of a small number of aberrant observations in a multisample binomial problem is studied; it is applicable to the fluctuation test when the protocol involves replicate measurements. Finally, the case of more than one positive dose of the test compound is investigated. Two statistical tests for this situation, both extensions of the one-tailed two-sample test, are extensively compared. A departure from monotonicity at high doses has a more serious effect on the power of the 'regression' test than on that of the 'isotonic' test. A variant of the isotonic test, based on the angular transformation, should be avoided. (Author abstract) (30 Refs)

62. DRUG ANTIMUTAGENESIS (REVIEW).

Zolotareva GN, Akaeva EA
Res. Inst. Biological Testing of Chemical Compounds, Moscow Oblast', USSR
Khim Farm Zh; 15(12):9-14 1981

The results of screening for chemical compounds that reduce the mutagenic properties of drugs but do not affect their therapeutic activity are reviewed. The group of compounds that reduce the level of chemical mutagenesis includes nucleic acids and their metabolites, natural metabolites (spermine, ATP, thiouracil, gibberellic acid), inhibitors of free radical reactions, acridine orange, dimethylsulfoxide, streptomycin, chloramphenicol, actinomycin D, hexamidine, and vitamins A, E. and C. It was emphasized that testing of the potential antimutagenic activity should be carried out in a number of test-systems and in a wide range of concentrations. (92 Refs) (In RUS)

63. MUTAGENS, CARCINOGENS AND THE WATER CYCLE.

Tye RJ, Waite WM, Bell WJ, Forster R, Blackmore D, Klemperer R, Starling D, Noone GP
Finham Regional Lab., Severn-Trent Water Authority, Severn-Trent, England
Water Pollut Control; 80(5):600-613 1981

Systems which are regarded as of potential application to the testing of chemicals in waters with emphasis on those systems used or proposed for use by the Severn-Trent Water Authority Mutagenicity Unit (STMU) are discussed. Currently the most widely used mutagenicity testing systems utilize bacteria as test organisms. The two species of bacteria most commonly used, Salmonella typhimurium and Escherichia coli, have been modified to increase their sensitivity in assays. Mammalian cell transformation assays using a line of hamster kidney fibroblast cells grown as monolayers on solid surfaces is probably the most promising non-bacterial testing system. Work in the STMU has been restricted to the study of organics, especially haloforms and polycyclic aromatic hydrocarbons, although they are not the only active constituents in water implicated in carcinogenesis. Approx 200 organic chemicals have been identified in water samples. The study shows that mutagenic responses may be induced by a wide range of both raw and treated waters using a tube-fluctuation test without prior concentration. Concentration of trace organics in water is discussed. Results of any bacterial mutagenicity assay show whether the test material can cause a statistically significant increase over the spontaneous rate at which mutations occur. Demonstration of bacterial mutagenesis is not a demonstration of hazard to human health. Mutagenesis testing can be applied either to natural water samples or to materials shown to be present in waters by analytical techniques and subsequently tested as pure substances. (17 Refs)

64. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

The carcinogenic risk to humans of some antineoplastic and immunosuppressive agents is reviewed and analyzed and areas in which additional research is needed. The compounds considered, include alkylating agents, antimetabolites, mitotic inhibitors, and/or immunosuppressants. Alkylating agents are generally carcinogenic and mutagenic and produced tumors at multiple organ sites. For most drugs, only case reports were available for study. Whenever possible, concern about late complications was considered. Monographs are presented on 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins, chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulphan, vinblastine sulfate, and vincristine sulfate. (1545 Refs)

65. MUTAGENICITY STUDIES OF VINYL CHLORIDE.

Fabricant JD, Legator MS
Dept. Preventive Medicine and Community Health, Div. Environmental, Toxicology Univ. Texas Medical Branch, Galveston, TX, 77550
Environ Health Perspect; 41:189-193 1981

Studies of the mutagenicity of vinyl chloride (VC) in man and test organisms are reviewed. In vitro studies have demonstrated mutagenicity in both prokaryotic and eukaryotic organisms. In vivo studies of cytogenetic effects in animals and humans have demonstrated somatic and germinal mutations. VC hazards and the consequences of mutations are discussed. (26 Refs)

66. DIRECT-ACTING MUTAGENS IN DIESEL EXHAUSTS: MAGNITUDE OF THE PROBLEM.

Rosenkranz HS
Center for Environmental Health Sciences, Case Western Reserve Univ., Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 101(1):1-10 1982

Widespread and increased use of diesel engines in the United States will be accompanied by an increase in particulate emissions with potential mutagenic and carcinogenic components. The major class of chemicals associated with the mutagenic effect of diesel emissions (DE) is the nitroarenes, particularly the nitropyrenes. DE mutagenic activity is in the range of 15 revertants/ug dichloromethane extract which can be translated into approx 1.25 x 10(6) revertants/g particulate emitted. 1-Nitropyrene (NP) appears to be the major mutagenic species and accounts for approx 20% of the mutagenic activity in DE;. the other 80% of activity may be caused by 1,8-dinitropyrene (DNP). Diesel particulate containing 93 and 1.5 ug of NP and DNP, respectively, may account for the observed mutagenic potencies of DE materials. However, lower estimates for the DNP contribution to the total direct-acting mutagenicity of DE extract have been reported. The United States estimated annual output of NP is 14,415 kg, and of DNP is 233 kg. When heavy-duty diesels are considered, such estimates would be increased 2.4-fold to determine the total amount of nitropyrenes released yearly. Nitropyrenes are not only mutagenic, but are carcinogenic in rodents. Development of a postcombustion process to reduce the amounts of nitropyrene particulate in DE is feasible and w arrants further study. Periodic, mandatory inspection of diesel-powered vehicles is advocated. (70 Refs)

67. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.

Kafer E, Scott BR, Dorn GL, Stafford R

Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada

Mutat Res; 98(1):1-48 1982

A critical summary of the 1965-1978 literature is made and background information on the test fungus is presented which covered a wider time period. Most of the reported test systems measured frequency of homo- or hemizygous segregants in heterozygous diploids. These could detect non-mutation genetic damage effects on spindles as well as a variety of types of mutations. However, the different procedures involved made for noncomparable results with the same chemical. Another test system measured increases in frequency of recessive lethals, or effects on recovery of haploid second-order segregants; it was similar to known tests in Drosophila. A third system measured effects on frequency of haploid sectors from duplication strains; it was limited by the availability of a single useful duplication strain. Results on 71 chemicals, including some antineoplastic agents and fungicides, were tabulated. Results of the more elaborate test systems pointed towards the appropriate mammalian system for higher level evaluation. More chemicals need to be tested to fully evaluate the utility of these three basic systems, and more experimental detail is needed on others. Emphasis was put on future use of positive and/or negative controls, full disclosure of results and procedures, use of more than one dose and/or adequate sample size, and proper statistical treatment. (97 Refs)

68. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR INDUCTION OF MITOTIC SEGREGATION AND MUTATION. II. HAPLOID ASSAY SYSTEMS AND OVERALL RESPONSE OF ALL SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.

Scott BR, Dorn GL, Kafer E, Stafford R

Phoenix, Lone Oak Lab., P.O. Box 744, Upton Road, Smithville, TX, 78957

Mutat Res; 98(1):49-94 1982

A critical evaluation of the 1965-1978 literature was made on the response of haploid Aspergillus systems to various agents, along with comparison to results obtained from in vivo carcinogenicity studies. Of the three test systems used, the methionine suppressor and 2-thioxanthine assays used multiallelic forward-mutations as a response to induced base-pair changes and small deletions while the arginine system used reverse mutations of unspecified nature. Only 1 false positive hit, was found in comparison of the 27 chemicals (of 124 listed) with known in vivo results. Two of the 24 positive chemicals required metabolic activation (mammalian), and 5 were nonmutagenic for Salmonella. Most of the methionine and 2-thioxanthine systems used the Glasgow biAl; methG1 strain, while the arginine system used the BIN-252 strain. The suggested protocol emphasized complete removal of germination-inhibitory substance, notation of use of germinated or quiescent nuclei, adequate dose/time/response testing, metabolic activation, 8-methoxypsoralen with and without UV as positive and negative control, and, for the methionine system, mandatory spontaneous background mutation frequency assay. A statistical method of data treatment was applied involving survival fraction correlation with mutation frequency. An advantage of the 2-thioxoanthine over the methionine system was assignability of mutants to specific gene loci. (76 Refs)

69. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.

Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

The range of biological methods which are used for the detection of mycotoxins was summarized, and their selectivity, sensitivity, and practicability were reviewed. Test organs included mouse leukemia cells and Hela cells, and the mycotoxins detected included aflatoxins. Carcinogenic mycotoxins have been detected through hepatoma formation in trout and various laboratory mammals and by the Ames mutagenicity system. The Ames test and similar ones were thought to be of little relevance to mycotoxin detection and serve mainly as indicators of mutagenicity or potential carcinogenicity. Findings showed that the existing bioassays are generally more subject to interference, less rapid and less reproducible than are chemical methods of detecting mycotoxins. (78 Refs)

70. CARCINOGENICITIES OF 3-METHOXY-4-AMINOAZOBENZENE, N-HYDROXY-3-METHOXY-4-AMINOAZOBENZENE AND RELATED AZO DYES IN THE MOUSE.

Watanabe HK, Hashimoto Y, Abe I, Sato H
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 73(1):136-140 1982

The carcinogenicities of 2-methoxy-4-aminoazobenzene and 3-methoxy-4-aminoazobenzene (2-MeO-AAB and 3-MeO-AAB) and their N-hydroxy derivatives (N-OH-2-MeO-AAB and N-OH-3-MeO-AAB) were tested in (C3H x C57BL/6) F1 mice. Topical sc injections, twice weekly for 8 wk, of 4 or 8 umol of N-OH-3-MeO-AAB dissolved in 0.1 ml of olive oil containing 10% dimethyl sulfoxide induced fibrosarcomas at the site of application. Similar treatment with 3-MeO-AAB or 2-MeO-AAB as well as N-OH-2-MeO-AAB failed to induce sarcomas. Oral administration of 0.09% 3-MeO-AAB in the diet for 13 mo induced hepatic tumors in female mice but not in males. 2-MeO-AAB did not induce tumors in male or female mice. The relationship between carcinogenicity, mutagenicity, the ability to induce unscheduled DNA synthesis, and the metabolism of these azo dyes is discussed. (Author abstract) (18 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
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Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
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6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
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8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
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Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
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Environ Health Perspect; 41:211-220 1981

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11. ALCOHOL AND CANCER.
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12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
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13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
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15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
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23. NONASBESTOS FIBROUS MINERALS.
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24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
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Cancer; 49(5):1056-1066 1982

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29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
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Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
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Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
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33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

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34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

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Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
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37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
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39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. **NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.**
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

SERIES CK19 No. 82/08

AUGUST, 1982

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TESTS FOR CELL TRANSFORMATION

1. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.

Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982

A great variety of practical short term tests for detecting potential carcinogenic chemicals have been proposed over the last 10 yr. Tests based on the cellular transformation of mammalian cells in culture are included in this group. After a brief review of the different characteristics of this transformation,

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the principal cell systems, the methods used and the results obtained by authors who developed and/or use these tests, are presented. It seems justified to include the simplest and most reliable of these tests in the battery of screening tests for the research of potential carcinogenic properties of chemicals. The present orientation of research, likely to lead to more discriminating tests, is discussed. (Author abstract) (220 Refs) (In FRE)

IN VIVO TESTS FOR MUTAGENICITY

2. THE USE OF LARVAL STAGES OF DROSOPHILA IN SCREENING FOR SOME NATURALLY OCCURRING MUTAGENS.

Clark AM
Sch. Biological Sciences, Flinders Univ. South Australia, Bedford Park, 5042, Australia
Mutat Res; 92(1/2):89-97 1982

The mutagenic effects of several naturally occurring substances were tested in X-linked recessive lethal assays in larval and adult male Drosophila. The substances tested were heliotrine, rutin, quercetin (rutin aglycone), juglone (5-hydroxy 1.4-naphthoquinone), bracken fern extract, and fresh or dried leaves of Russian comfrey (Symphyton officinale). Extracts of fresh comfrey leaves were mutagenic in the Drosophila test, but the dried leaves were not. The results suggested that comfrey tea (widely promoted in health food stores) is unlikely to pose a mutagenic hazard to humans, although this may not be the case for fresh comfrey leaves used in salads. In general, the larval stages (notably the third-instar stage) were more susceptible to the mutagenic effects of these substances than the adult males. If this higher sensitivity is based on metabolic activation by the fat body, this would imply the passage of metabolites from fat body cells to the larval testis. Further tests with a wider range of mutagens are required to evaluate the tentative conclusion that Drosophila larvae are often more sensitive than adults for screening purposes. Both larval and adult stages should be tested before it is concluded that a suspected mutagen is inactive in the Drosophila sex-linked recessive lethal test. (28 Refs)

3. A SEARCH FOR SOME COMMON CHARACTERISTICS OF THE EFFECTS OF CHEMICAL MUTAGENS IN DROSOPHILA.

Vogel EW, Blijleven WG, Kortselius MJ, Zijlstra JA
Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratoria, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 92(1/2):69-87 1982

An analysis of shared general features was used to compare the actions of mutagens in Drosophila. Germ cell metabolism is the most significant factor determining the effects of promutagens in various cell stages. Only autosomal recessive lethal mutations can be used to compare stages of sensitivity to a given mutation. Only a few mutagens have been tested in both sexes of Drosophila, including mitomycin C, bleomycin (BLM), and diethylstilbestrol. Females are much more sensitive than males to the mutagenic action of BLM, which causes recessive lethals and X-chromosomal aneuploidy in oocytes. The mutagenicities of some (not all) alkylating agents can be greatly modified by introducing repair-deficient mutants into the test system, but each new strain must be validated before it is tested with a wide variety of mutagens. The molecular mechanisms of the interactions of some methylating and ethylating agents with DNA are related to their genetic effects in germ cells. The relative proportions of chromosome aberrations to mutations and the ability of an agent to induce delayed mutations can be used to provide more information on the basic mechanisms of chemical mutagenesis. For at least some mutagens, a positive correlation has been discovered between the induction of chromosome aberrations in germ cells and the induction of an increased proportion of mosaic twin spots (relative to mosaic single spots) in somatic tissues. (68 Refs)

4. SUPERMUTAGENICITY OF ETHYLNITROSOUREA IN THE MOUSE SPOT TEST: COMPARISONS WITH METHYLNITROSOUREA AND ETHYLNITROSOURETHANE.

Russell LB, Montgomery CS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 92(1/2):193-204 1982

The embryotoxicities and mutagenicities of ethylnitrosourea (ENU: 25-100 mg/kg), methylnitrosourea (MNU: 5-7.5 mg/kg), and ethylnitrosourethane (NEC: 100-150 mg/kg) were studied in (C57BL/R1 x multiple-recessive T)F1 mice. Female C57BL/R1 mice were treated with the agent on day 9 or 10 of pregnancy. The spot test was used to obtain information on mutations, cytotoxicity (the occurrence of white midventral spots during the first 7 wk after birth), and teratogenic effects. For all endpoints studied, ENU was more effective than NEC. Compared to MNU, ENU was less toxic, less teratogenic, and less mutagenic in the spot test but more mutagenic in spermatogonia and a much stronger transplacental carcinogen than MNU. MNU is apparently a stronger inducer a gross chromosomal damage than ENU, whereas ENU causes more gene mutations than MNU. Both types of mutational damage are evident on the spot test; gene mutations are evident from spermatogonial studies. (20 Refs)

5. AN IN VIVO METHOD FOR THE DETECTION OF SOMATIC MUTATIONS AT THE CELLULAR LEVEL.

Searle AG, Stephenson DA
Radiobiology Unit, Medical Res. Council, Harwell, Oxon OX11 0RD, England
Mutat Res; 92(1/2):205-215 1982

In mice, recessive mutations at the autonomous dilute (d) and leaden (ln) loci change the shape of pigment cells in the hair follicles; individual mutant melanocytes can be recognized in the dorsal skin after the postnatal onset of melanogenesis. Mice heterozygous for d and ln were exposed to x-rays (0-200 rads) or procarbazine (PCB: 0-300 mg/kg, ip) by maternal treatment on day 17 of pregnancy. Both treatments caused an increase in the frequencies of visible melanocytic mutations. The dose-response curves for both treatments were consistent with a square-law response. The mutagenic effects of x-rays (100 rads) and PCB were consistent with those reported for the spot test. (26 Refs)

6. STUDIES ON THE MUTAGENIC POTENTIAL OF THE PESTICIDE CHLORDIMEFORME AND ITS PRINCIPAL METABOLITES IN THE MOUSE HERITABLE TRANSLOCATION ASSAY.

Lang R, Adler ID
Res. Lab., Schering, Berlin/Bergkamen, W. Germany
Mutat Res; 92(1/2):243-248 1982

Random-bred NMRI/SPF male mice were treated for 7 wk (by gavage) with max tolerated doses of chlordimeforme (CDMF: 120 mg/kg/day) or one of its principal metabolites, N-formyl-4-chloro-o-toluidine (100 mg/kg/day) and 4-chloro-o-toluidine (200 mg/kg/day), then mated with untreated females. The treated mice and male F1 offspring were screened for fertility. Animals showing reduced fertility or sterility were examined cytogenetically, by scoring meiotic chromosomes for translocation multivalents or assessing mitotic cells for marker chromosomes. CDMF and both of its principal metabolites at toxic doses did not induce translocation heterozygosity. The positive control agent, triethylene melamine (0.05 mg/kg/day), gave the expected mutagenic response. (7 Refs)

7. INDUCTION OF SPECIFIC-LOCUS MUTATIONS IN FEMALE MICE BY TRIETHYLENEMELAMINE (TEM).

Cattanach BM
M.R.C. Radiobiology Unit, Harwell, Didcot, Oxon OX11 ORD, England
Mutat Res; 104(1-3):173-176 1982

A test for point-mutation induction in mouse oocytes was conducted following treatment of female mice with triethylenemelamine (TEM). TEM (2.0 mg/kg ip) was administered to F1 hybrid (C3H/HeH x 101/H) female mice. Immediately after treatment the females were placed with tester stock PT males. Offspring from resultant litters were scored when 3 wk old for mutations at seven specific loci and also for dominant visible mutations. Two specific-locus mutations and one new dominant visible mutation were recovered from a total of 10,812 offspring. The specific-locus mutation frequency was approx 2.64 x 10(-5)/locus/gamete. From the dates of birth of the two specific-locus mutants, it was deduced that both must have been conceived within the first 2 days of treatment of mothers. When data were weighted for dose, the sensitivity of the mature oocyte to TEM appeared similar to that of spermatogonial stem cells. The specific-locus mutations produced by TEM in oocytes are unlikely to result from chromosomal rather than genic changes, since both mutations have proved to be homozygous viable. (18 Refs)

8. EVALUATION OF MUTAGENIC ACTIVITY OF COOKING OIL VAPORS BY MOUSE SPERM ABNORMALITY TEST.

Kam JK
P.O. Box 527, Whittier, CA, 90608
Environ Res; 27(2):261-265 1982

Three brands of commercial cooking oil were simmered to evaporation on 23-cm-diameter frying pans. The oil vapors were collected on silica gel and activated charcoal adsorption columns. The samples were desorbed by acetone and carbon disulfide, respectively. Mouse sperm abnormality tests revealed no mutagenic activity. (Author abstract) (17 Refs)

9. EXPRESSION OF GENETIC DAMAGE INDUCED BY ALKYLATING AGENTS IN GERM CELLS OF FEMALE MICE.

Becker K, Schoneich J
Zentralinstitut fur Genetik und Kulturpflanzenforschung, Akademie der Wissenschaften der DDR, 4325 Gatersleben, E. Germany
Mutat Res; 92(1/2):447-464 1982

The effects of trenimon (TR: 0.25 or 1 mg/kg, ip) and cyclophosphamide (CP: 150 mg/kg, ip) on germ cells were studied in female random-bred NMRI mice (10-13 wk old). Pre-ovulatory treatment with CP or the higher dose of TR caused an increase (significant with TR, slight with CP) in frequency of meiotic non-disjunction in the unfertilized oocytes but did not cause structural aberrations in second-metaphase oocytes. In mice treated with CP or the lower dose of TR before ovulation and mated with random-bred NMRI males up to 0.5 day after treatment, TR showed a strong clastogenic effect on the first-cleavage embryos (first-cleavage metaphase). Numerical and structural chromosome aberrations were observed in 63.39% of the embryos; most of the aberrations were structural aberrations of the chromatid types. The embryonic mortality rate was 55.17%, as measured in the dominant lethal assay. Similar treatment with CP enhanced the occurrence of dominant lethal effects to 58.94%. When the alkylating agents were given at longer times before mating (up to 23.5 days), their clastogenic and mutagenic effects declined with time. The results observed with TR support the conclusion that an intervening round of DNA replication is required for TR-induced DNA damage to be transformed into a structural aberration. (55 Refs)

10. ON THE NATURE OF PARTIAL LOSSES OF THE Y CHROMOSOME FROM TREATMENT OF RING-X/BSYY+ MALES WITH DIETHYLNITROSAMINE (DEN) OR PROCARBAZINE AND MATING WITH REPAIR-DEFICIENT ST MUS302 FEMALES OF DROSOPHILA.

Zimmering S, Kammermeyer KL
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Mutat Res; 104(1-3):121-123 1982

The nature of partial losses of the Y chromosome after treatment with diethylnitrosamine (DEN) or procarbazine (PCARB) was studied in Drosophila melanogaster. Xc2,yf/BSYy+ males approx 24 hr old were starved for 6 hr. They were then left untreated or treated with 10 milliM (mM) DEN or 5 mM PCARB. Treated and untreated males were then mated with y as sc;st mus302 females. F1 progeny were classified as regular females (y), regular males (sc B), loss of X or Y (principally loss of ring-X: y ac sc male), loss of BS (sc male), loss of y+ with loss of ac+ (y ac sc B male), loss of y+ without loss of ac+ (y sc B). Loss of y+ was accompanied by loss of ac+ in 15/16 losses produced by DEN and 50/50 losses produced by PCARB. All y ac sc B males showed reduction in eye size consistent with homozygous BS phenotype, indicating interchange of Y-arms. Crosses of ring-X/BSYy+ males with RM(1)y2,su-wa wa bb/o;st mus302 females produced six females carrying the BSY fragment. The BSY fragment was placed in combination with an X.Y chromosome and tested for wild-type alleles of ac and lethal259. One fertile male was obtained; no evidence of either wild-type allele was found. Two fertile males carrying the X.Y/BSY fragment were obtained from crosses of ring-X/BSYy+ males treated with DEN and X.Y,y/y w;st mus302 females. Neither of these males showed evidence of the wild-type alleles. Three other losses of y+ were accompanied by loss of adjacent markers. Thus 18/19 losses of y+ after DEN treatment were apparently produced by chromosome breakage. All or nearly all partial losses of the BSYy+Y chromosome after treatment with DEN or PCARB were attributed to chromosomal breakage. (10 Refs)

11. THE EFFECT OF BENZO[A]PYRENE ON SPONGES AS MODEL ORGANISMS IN MARINE POLLUTION.

Zahn RK, Kurelec B, Zahn-Daimler G, Muller WE, Rijavec M, Batel R, Given R, Pondeljak V, Beyer R

Physiologisch-Chemisches Institut, Johannes-Gutenberg-Universitat, Duesbergweg, D-6500 Mainz, W. Germany

Chem Biol Interact; 39(2):205-220 1982

The majority of the investigations were performed with the marine sponge Tethya lyncurium at concentrations of 2 x 10(-8) to 1 x 10(-11) g/ml of benzo[a]pyrene (BaP). Sea-pollution was characterized as BaP equivalent activity in the Ames test. Increased activity of ornithine decarboxylase (ODC) was observed when sponges were artificially exposed at polluted marine areas for 3 wk. In contrast, to the situation in higher animals no ODC induction of the fast type was observed. Mixed function oxygenases (MFO) were not detected in sponges no could they be induced as in vertebrates. BaP was absorbed by Tethya and concentrated 30-60 fold. In live, but not dead, artificially perfused sponged [3H]- and [14C]BaP-radiolabel became firmly associated with DNA, RNA and protein of the sponges. The association persisted in isolated fractions, in nucleotides, in nucleosides and in protein hydrolysates. The BaP binding ratio to DNA was found to be strongly correlated to the concentration of BaP. Light modifiers BaP and thus enables binding. In the dark only very low association, if any, is observed. The possible consequences of these findings are discussed. (Author abstract) (48 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

12. EFFECT OF TEMPERATURE ON MUTATION IN CULTURED HUMAN SKIN FIBROBLASTS.

Simons JW

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, P.O. Box 9503, 2300 RA Leiden, The Netherlands

Mutat Res; 92(1/2):417-426 1982

Normal human diploid skin fibroblasts were tested for mutation towards hypoxanthine guanine phosphoribosyltransferase (HPRT-) deficiency after exposure to different temperatures (31-40 C) in medium containing azaserine (AZS: HAT or HAT-adenine media). Cultivation in HAT medium (performed to delete preexisting mutants) was highly mutagenic. The results of some experiments suggested that AZS acted as an indirect mutagen. The process of AZS mutagenesis was highly temperature-dependent; the frequency of HPRT- mutants/cell generation increased 10x as the temperature was increased from 33-37 C. The temperature dependence, if used as a starting point for estimating the consequence of an increase in gonadal temperature, might be responsible for a 135% increase in incidence of the sex-linked lethal HPRT- disease (Lesch-Nyhan syndrome) in the human population. Available epidemiologic data on the frequency of Lesch-Nyhan syndrome and the ratio of paternal and maternal mutation leading to the disease do not contradict the results on effects of temperature on mutation rate. (14 Refs)

13. CELL-MEDIATED MUTAGENICITY IN CHINESE HAMSTER V79 CELLS OF DIBENZOPYRENES AND THEIR BAY-REGION FLUORINE-SUBSTITUTED DERIVATIVES.

Hass BS, McKeown CK, Sardella DJ, Boger E, Ghoshal PK, Huberman E

Toxicology Dept., Shell Development Co., Westhollow Res. Center, Box 822, Houston, TX, 77001

Cancer Res; 42(5):1646-1649 1982

The polycyclic aromatic hydrocarbons dibenzo(a,i)pyrene and dibenzo(a,h)pyrene, each of which possesses two bay regions, and their bay-region difluorinated derivatives were tested for mutagenicity for ouabain and 6-thioguanine resistance in Chinese hamster V79 cells. Since V79 cells do not metabolize polycyclic aromatic hydrocarbons, mutagenesis was tested in both the presence and the absence of golden hamster embryo cells capable of metabolizing polycyclic aromatic hydrocarbons. Neither of the dibenzopyrenes nor their fluorinated derivatives were mutagenic in the absence of the golden hamster embryo cells. In the presence of these cells (cell-mediated assay), both dibenzopyrenes were mutagenic, whereas the difluorinated derivatives, 2,10-difluorodibenzo(a,i)pyrene and 3,10-difluorodibenzo(a,h)pyrene, either were inactive or exhibited (on a dose basis) a weak response. However, the mutagenicity of the dibenzopyrenes was eliminated when they were coincubated with 7,8-benzoflavone, a mixed-function oxidase inhibitor. The results suggest that metabolic oxidation of these polycyclic aromatic hydrocarbons at the bay region (presumably to diol-epoxides) is required for a mutagenic response in the cell-mediated assay. (Author abstract) (39 Refs)

14. ABSENCE OF MUTAGENIC ACTIVITY OF THREE FORMS OF ASBESTOS IN LIVER EPITHELIAL CELLS.

Reiss B, Solomon S, Tong C, Levenstein M, Rosenberg SH, Williams GM

Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY, 10595

Environ Res; 27(2):389-397 1982

The amosite, crocidolite, and chrysotile forms of UICC asbestos were assayed for their ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase locus. Using adult rat liver-derived (ARL-6 and ARL-18) cells in culture, no consistent or significant increase occurred in the number of mutants resistant to the purine analog, 6-thioguanine, after exposure to toxic levels of amosite, crocidolite, or chrysotile. These results support the concept that asbestos is an epigenetic carcinogen that does not alter DNA. (Author abstract) (55 Refs)

15. DIFFERENCES IN TEMPORAL ASPECTS OF MUTAGENESIS AND CYTOTOXICITY IN CHINESE HAMSTER CELLS TREATED WITH METHYLATING AGENTS AND THYMIDINE.

Peterson AR, Peterson H

Cancer Center, Dept. Microbiology, Univ. Southern California, Cancer Res. Lab., 1303 N. Mission Road, Los Angeles, CA, 90033

Proc Natl Acad Sci USA; 79(5):1643-1647 1982

Equitoxic concentrations of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and methyl methanesulfonate (MeMes) produced different frequencies of 5-azaguanine-resistant mutants and different amounts of N7-methylguanine, O6-methylguanine (m6G), and N3-methyladenine in the DNA of V79 Chinese hamster cells. Thus, neither the cytotoxicities nor the mutagenicities of these methylating agents could be attributed solely to nitrogen or to oxygen methylations in the DNA. However, MNNG produced 12-fold more m6G and 5-fold more mutants than did MeMes, indicating that a substantial part of the MNNG-induced mutations resulted from m6G-thymine mispairing during DNA replication. The expression as mutants of mutagenic oxygen methylations in the DNA of cells treated with MNNG was enhanced by thymidine (dThd) and deoxycytidine (dCyd), but these nucleosides did not significantly enhance MeMes-induced mutagenesis. The cytotoxicities of MNNG and MeMes were also increased by 10 uM dThd in proportion to the amount of m6G in the DNA. These increases in cytotoxicity were abolished by dCyd, which did not greatly reduce the dThd-induced enhancements of mutagenesis. Moreover, when dThd was present only during the 2-hr treatment with MNNG, maximal cytotoxicity occurred, but MNNG-induced mutagenesis was not increased. Maximal mutagenesis occurred when the dThd was present throughout the first doubling time of the MNNG-treated cells. Thus, the expression of the cytotoxicity and the mutagenicity associated with m6G in the DNA of V79 cells occurred by quite different mechanisms. (Author abstract) (31 Refs)

16. INHIBITION OF METABOLIC COOPERATION IN CHINESE HAMSTER V79 CELLS IN CULTURE BY VARIOUS POLYBROMINATED BIPHENYL (PBB) CONGENERS.

Tsushimoto G, Trosko JE, Chang CC, Aust SD
Dept. Pediatrics and Human Development, Coll. Medicine, Michigan State Univ., East Lansing, MI, 48824
Carcinogenesis; 3(2):181-185 1982

Using an in vitro assay system to measure a form of cell-cell communication in Chinese hamster V79 cells, several purified polybrominated biphenyl (PBB) congeners were analyzed for their ability to affect colony-forming ability and 'metabolic cooperation' in these cells. Results clearly demonstrate the assay's ability to distinguish differences in the cytotoxic and metabolic cooperation-inhibiting properties of these congeners related to their structure. It appears that if a carbon ortho to the bridge carbon of each phenyl ring is brominated, the molecule has the property by which metabolic cooperation is inhibited. The results suggest that several PBB congeners share at least one property associated with several known tumor promoters, such as the phorbol esters. Although we have not ruled out that the mixture of PBB congeners might contain initiators or that various PBB metabolites would be mutagen/initiators, based on these and other results, it was concluded that the reported carcinogenic potential of PBB seems to be mediated by its action as a tumor promoter, rather than as a complete carcinogen or an initiator. (Author abstract) (54 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

17. THE CHEMICAL ACTIVATION OF NON-MUTAGENIC NITRATED POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENS.

Karpinsky GE, McCoy EC, Rosenkranz HS
Center for the Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 92(1/2):29-37 1982

Ames assays in Salmonella strains TA1535, TA100, TA98, and nitroreductase (NRase)-deficient strains TA100NR and TA98NR were performed with 5-nitroquinoline (5-NQ), 6-nitroquinoline (6-NQ), 8-nitroquinoline (8-NQ), 1,8-dinitronaphthalene (1,8-DNN), 1-5-dinitronaphthalene, 4-nitroquinoline 1-oxide, 2-nitrofluorene, and nitrofurantoin, in the presence or absence or rat liver microsomes (S9 mix). Both 5-NQ and 6-NQ were direct-acting bacterial mutagens, but 8-NQ (a carcinogen in rats) and 1,8-DNN (an analog of 8-NQ) were not mutagenic even in the presence of S9 mix. The non-mutagenicity of 8-NQ and 1,8-DNN could be overcome chemically, in situ, by the addition of zinc (Zn) dust. Anaerobic conditions were not required for a max yield of the mutagenic product of 1,8-DNN. The mutagenicity of the 1,8-DNN product was not due to a nitro function, as shown by the fact that it was fully active even in the NRase-deficient strain TA100NR. It is concluded that although bacteria can reduce some nitrated polycyclic aromatic hydrocarbons (N-PAH) to mutagens, their NRases cannot reduce the nitro functions of all N-PAHs to the proximate mutagenic hydroxylamines. Chemical reduction of the N-PAH (ie, non-enzymatic activation) with Zn (which is compatible with the Ames bioassay) may be a useful addition to the procedure in the evaluation of the potential mutagenicity of nitro-containing chemicals. (24 Refs)

18. AN EVALUATION OF THE GENOTOXIC PROPERTIES OF INSECTICIDES FOLLOWING PLANT AND ANIMAL ACTIVATION.

Gentile JM, Gentile GJ, Bultman J, Sechreist R, Wagner ED, Plewa MJ
Dept. Biology, Hope Coll., Holland, MI, 49423
Mutat Res; 101(1):19-29 1982

Commercial grades (CG) and technical grades (TG) of two carbamate, six organophosphate, and two chlorinated hydrocarbon insecticides were tested for genotoxicity in Salmonella typhimurium and Saccharomyces cerevisiae with rat liver metabolic activation (S9), plant metabolic activation (maize 1S fractions), or no activation. CG of each insecticide was also tested for mutations at the waxy (wx) locus of Zea mays. Carbofuran, metham, curacron, phorate, and chlorpyrifos were negative in all assays. CG and TG fonofos were mutagenic to Salmonella following S9 activation and TG fonofos was weakly positive in the S cerevisiae assay. TG terbufos was recombinogenic in S cerevisiae both directly and with S9 activation, while CG was weakly recombinogenic when tested directly. Field formulation of ethoprop was mutagenic in the maize wx assay. TG heptachlor was mutagenic to Salmonella with S9 activation. Both CG and TG chlordane were recombinogenic to Saccharomyces following S9 activation. Both heptachlor and chlordane were genotoxic following 1S activation and both were mutagenic in the maize wx assay. Mammalian microsomal activation systems should be complemented with plant activation systems in order to provide a comprehensive analysis of the genotoxic potential of agricultural agents. (26 Refs)

19. MUTAGENICITY SCREENING OF CRUDE DRUGS WITH BACILLUS SUBTILIS REC-ASSAY AND SALMONELLA/MICROSOME REVERSION ASSAY.

Morimoto I, Watanabe F, Osawa T, Okitsu T, Kada T
Saitama Inst. Public Health, Kamiokubo 639-1, Urawa-shi, Saitama-ken 338, Japan
Mutat Res; 97(2):81-102 1982

The mutagenicity of 104 commercial crude drugs (plant extract) was studied using the Bacillus subtilis rec-assay and the Salmonella/microsome reversion assay (Ames strains TA98 and TA100). The rec-assay disclosed mutagenic activity for

13/104 water extracts and 27/104 methanol extracts. The Ames assays (with or without metabolic activation) disclosed mutagenic activity for 24/104 water extracts and 16/104 methanol extracts. In all, 45/104 crude drugs showed mutagenic activity. (14 Refs)

20. ANALYSIS OF A METHOD FOR TESTING AZO DYES FOR MUTAGENIC ACTIVITY IN SALMONELLA TYPHIMURIUM IN THE PRESENCE OF FLAVIN MONONUCLEOTIDE AND HAMSTER LIVER S9.

Prival MJ, Mitchell VD
Genetic Toxicology Branch, Food and Drug Admin., Washington, DC, 20204
Mutat Res; 97(2):103-116 1982

A protocol was developed for assessing the mutagenicity of azo dyes derived from mutagenic or potentially mutagenic aromatic amines in Salmonella typhimurium TA98. In the protocol, uninduced hamster liver S9 (150 ul) is used instead of Aroclor 1254-induced rat liver S9 (max, 50 ul) in the standard assay; flavin mononucleotide is used instead of riboflavin to reduce the azo compounds to free amines; the cofactor mix is modified to include exogenous glucose 6-phosphate dehydrogenase, NADPH, and 4x the standard amount of glucose-6-phosphate; and 30 min of preincubation is performed before the top agar is added. All of the modifications were necessary for optimal mutagenic activity of the azo dyes tested: Congo red (CR), benzopurpurine 4B (BP4B), trypan blue (TB), and Direct Blue 1 (DB1). The assay was also performed using known or probable reduction products of the dyes having known mutagenic and carcinogenic activity: benzidine (BZD; a reduction product of CR), o-tolidine (o-TD: a reduction product of BP4B and TB), and o-dianisidine (o-DAD: a suspected reduction product of DB1). The mutagenicities of CR, TB, and DB1 were greater when hamster liver S9 was substituted for rat liver S9. BZD was more mutagenic with hamster liver S9 than with rat liver S9, but o-TD and o-DAD were not. Rat liver S9 inhibited the ability of hamster liver S9 to activate BZD to a mutagen. The presence in rat liver S9 of an inhibitor of BZD metabolic activation may account for the failure of BZD and a BZD dye (CR) to be strongly mutagenic in the presence of rat liver S9. (27 Refs)

21. MUTAGENICITY AND TOXICITY OF AFLATOXIN PRECURSORS.

Dunn JJ, Lee LS, Ciegler A
(c/o Lee) P. O. Box 19687, New Orleans, LA, 70179
Environ Mutagen; 4(1):19-26 1982

The Salmonella/microsome test and chick embryo test were used to determine the toxicity and mutagenicity of five aflatoxin B1 (AFB1) precursors: norsolorinic acid, averantin, averufin, versicolorin A and sterigmatocystin. A definite pattern emerged which indicated that the nearer to AFB1 an intermediate appears in the biosynthetic pathway, the greater is its mutagenicity and toxicity. (19 Refs)

22. MUTAGENICITY OF HPLC FRACTIONS FROM EXTRACTS OF AATREX-TREATED CORN.

Singh I, Lusby AF, McGuire PM
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Environ Mutagen; 4(1):45-53 1982

Water-imbibed kernels of hybrid corn were incubated in water containing 0, 30, 60 and 90 ppm of the herbicide AAtrex (80W), the active ingredient of which is atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine). At the 3-leaf stage, the plants were harvested and homogenized in five volumes of distilled water. The homogenate was filtered and centrifuged at 2,500 x gravity for 10 min. The crude extracts were tested for induction of gene conversion in a diploid (D4) strain of Saccharomyces cerevisiae heteroallelic at two loci; the strain requires adenine and tryptophan for growth. The extracts were subjected to analysis by high pressure liquid chromatography, and fractions collected in water, 50% and 100% methanol were similarly analyzed. AAtrex alone did not induce conversion. There was a clear dose response at both loci with the 50% methanol extract, indicating that some of the mutagenic activity resulted from interaction between the plant and herbicide. The 50% methanol fraction induced more conversion at 10 mg/ml than did the crude extract at twice the concentration. The study indicates that AAtrex-treated germinating corn contains more mutagen than controls. (44 Refs)

23. MUTAGENIC ACTIVITY OF STERILIZATION INDICATORS.

Atherholt TB, McGarrity GJ, Louis J
Dept. Microbiology, Inst. Medical Res., Camden, NJ, 08103
Environ Mutagen; 4(1):93-101 1982

Following initial studies that showed mutagenic activity in extracts of unspiked, sterile, deionized water, the Ames Salmonella microsomal assay was used to determine the source of mutagenicity in the materials and reagents used in these experiments. Mutagens were detected in acetone-methylene chloride extracts of black threads on glass tube-type sterilization indicators used in hospitals and laboratories and in extracts of commercially available black thread. Fluids autoclaved with these sterilization indicators may alter the results in mutagenicity and other studies. (12 Refs)

24. GENETIC TOXICOLOGY STUDIES WITH 2-NITROBENZOFURANS AND 2-NITRONAPHTHOFURANS.

Weill-Thevenet N, Buisson JP, Royer R, Hofnung M
Unite de programmation moleculaire et toxicologie genetique, CNRS, L.A. 271, INSERM U 163, Institut Pasteur, 28 rue du Docteur Roux, 75015 Paris, France
Mutat Res; 104(1-3):1-8 1982

The mutagenic activity of three 2-nitronaphtho[2,1-b]furans, two 2-nitronaphtho[3,2-b]furans, and two 2-nitronaphtho[1,2-b]furans was tested using the Salmonella/microsome assay (Mutatest). The seven compounds gave a mutagenic response with the following characteristics: it occurs on strains TA1537, TA1538, TA98, and TA100, but not no strain TA1535; the mutagenic response is partially dependent on the bacterial nitroreductase activity and is lower in the presence of an activating mixture S9 from rat liver; it varies quantitatively and qualitatively with the structure of the compound. The mutagenic responses of the 2-nitronaphthofurans and three 2-nitrobenzofurans was also examined in a phage-induction assay (Inductest). The mutagenic potency measured in the Mutatest correlated well with that measured by the Inductest; those compounds which were negative in the Mutatest were also negative in the Inductest. The mutagenic activity of the two most potent mutagens examined was tested using strains TA1978 and TA2421, the UVr+ counterparts of the TA1538 and TA98 uvrB excision-repair mutants used in the Mutatest. The mutagenic response was reduced by at least a factor of 100 compared to the uvrB mutants, indicating that the excision-repair system is efficient in preventing the mutagenic effect of the 2-nitronaphthofurans. 2-Nitro-7-methoxynaphtho[2,1-b]furan (R7000), one of the most potent compounds, also induced sperm abnormality in mice (Spermatest). The results of the bacterial tests and Spermatest in relation to the possible genetic toxicity of these compounds is discussed. (11 Refs)

25. TEST-CONDITION-DEPENDENT INFLUENCE OF HARMAN AND NONHARMAN ON BENZO[A]PYRENE MUTAGENESIS IN SALMONELLA.

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Mutat Res; 104(1-3):9-15 1982

The influence of harman and norharman on benzo[a]pyrene [BaP] mutagenicity was examined under various experimental conditions in the Ames test to elucidate contradictory reports of mutagenic, co-mutagenic, and non-mutagenic activities of the compounds. Conditions varied were the nature and amount of metabolizing system (S9) preparation, amount of co-factors, and relative proportion of test chemicals. Harman and norharman were not mutagenic using this test system. Activation by 3-methylcholanthrene-, phenobarbital-, and Aroclor 1254-induced mouse liver homogenates led to decreased mutagenicity of BaP in Salmonella typhimurium TA98 upon addition of harman or nonharman. Under conditions of activation by Aroclor 1254 induced rat liver homogenate, harman increased BaP revertants while norharman did not affect BaP mutagenicity. Using phenobarbital-induced mouse liver homogenate, varying the S9 extract amount, the amount of cofactors, or the relative proportions of test substances, within certain limits, had no effect on harman or norharman antagonism of BaP mutagenesis. While the Ames test is valuable in qualitatively determining mutagenicity/non-mutagenicity of single chemicals, different S9 extracts can yield widely varying results when assessing the possible synergistic or antagonistic effects of further chemicals. (8 Refs)

26. CONTRIBUTION OF 1-NITROPYRENE TO DIRECT-ACTING AMES ASSAY MUTAGENICITIES OF DIESEL PARTICULATE EXTRACTS.

Salmeen I, Durisin AM, Prater TJ, Riley T, Schuetzle D

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Mutat Res; 104(1-3):17-23 1982

The percentage contribution [P] of 1-nitropyrene [1-NP], a derivative of the carcinogenic polycyclic aromatic hydrocarbons, to the direct-acting Ames Salmonella assay mutagenicities of extracts of exhaust particles collected from three different diesel powered vehicles was assessed. 1-NP was shown to be a substantial contributor to the Ames assay mutagenicities for the three diesel particulate extracts examined. For Salmonella strains TA98, TA100, and TA1538, respectively, P was 16, approx 1, and 7% for one vehicle (1-NP = 2,030 +-220 ppm); 24, 9, and 17% for the second vehicle (1-NP = 150 +-30 ppm); and 13, 4, and 13% for the third vehicle (1-NP = 55 +-11 ppm). Using this assay system, even a 1% contribution of a single compound is important, considering the several hundreds of compounds present in the particulate extracts. Salmonella-histidine reversion assays indicated that the extract matrix had little effect on the mutagenicity of 1-NP. The significance of diesel exhaust-associated 1-NP in relation to adverse effects on human health was discussed. (22 Refs)

27. ABSENCE OF GENOTOXICITY INDUCED BY 3H AND 14C LABEL IN SALMONELLA TYPHIMURIUM AND BACILLUS SUBTILUS.

Gentile JM, Gaff S, Gentile GJ, Townsend S, Means JC, Plewa MJ
Dept. Biology, Hope Coll., Holland, MI, 49423
Mutat Res; 104(1-3):29-33 1982

The possible mutagenic effects due to the presence of either 3H or 14C in a normally nonmutagenic agent was studied using the Salmonella typhimurium and the Bacillus subtilus rec assays. The chemicals studied included tryptophan, leucine, inulin, guanosine, thymidine, and 3H2O. The presence of either label on a compound did not affect standard microbial genotoxin assays and will probably not cause an enhanced genetic effect when used in combination with a mutagen. (17 Refs)

28. DIURNAL VARIATIONS IN THE MUTAGENICITY OF AIRBORNE PARTICULATE ORGANIC MATTER IN CALIFORNIA'S SOUTH COAST AIR BASIN.

Pitts JN, Harger W, Lokensgard DM, Fitz DR, Scorziell GM, Mejia V

Statewide Air Pollution Res. Center, Univ. California, Riverside, CA, 92521

Mutat Res; 104(1-3):35-41 1982

Diurnal variations in the mutagenicity of ambient particles collected simultaneously near downtown Los Angeles, California and at two downwind sites were examined to determine both the sources and ambient levels to which urban and suburban human populations may be exposed. Collections were made every 3 hr for a 24-hr period on two late summer days in 1980 and an early spring day in 1981 and assessed for mutagenicity using the Ames assay (using Salmonella strains TA98 and TA98NR). Ambient particulate mutagenicity displayed primary pollutant characteristics, responding both to vehicular emission rates and to atmospheric mixing ratios as shown by high correlation with CO, NOx and Pb levels. Results indicated that short-term peak mutagen densities can be much higher than the commonly reported 24-hr av. Nitroarenes may contribute substantially to the mutagenicity of ambient particulate matter in the study area. Chemical transformations of mutagenic material collected on the filters are apparently either very fast or very slow relative to the time scale used in these experiments. The increased contribution of promutagenic activity to the mutagenicity of the particles during periods of high emission rates, and its subsequent return to lower levels relative to direct activity, suggest that some promutagenic materials present in freshly emitted particulate organic matter are subject to rapid destruction in the atmosphere. (27 Refs)

29. MUTAGENICITY AND DNA-MODIFYING ACTIVITY OF 2-NITROPROPANE.

Speck WT, Meyer LW, Zeiger E, Rosenkranz HS
Dept. Pediatrics, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 104(1-3):49-54 1982

DNA-modifying activity and mutagenicity of the industrial solvent 2-nitropropane and also 1-nitropropane, 1-aminopropane, and 2-aminopropane were examined. Using the Salmonella typhimurium mutagenicity assay, 2-nitropropane was shown to be mutagenic, 1-nitropropane had marginal activity, and 1- and 2-aminopropane were not mutagenic. Only 2-nitropropane showed DNA-modifying activity. The mutagenic, and presumably carcinogenic, effects of 2-nitropropane may be due in part to a direct, non-enzymic, reaction between the chemical and intracellular DNA. (10 Refs)

30. MUTAGENICITY OF NIFURPIRINOL (P-7138) IN ESCHERICHIA COLI WP2 AND SALMONELLA TYPHIMURIUM TA100.

Nakamura Y, Fukushima H, Tomita I, Kimura I
Lab. Health Science, Shizuoka Coll. Pharmaceutical Sciences, Shizuoka-422, Japan
Mutat Res; 104(1-3):61-66 1982

The mutagenicity of nifurpirinol (NP) was examined using UV-repair-competent and -deficient strains of Escherichia coli B/r WP2 and the Salmonella typhimurium strain TA100 in the absence of rat microsomal activation system (S9 mix). The modified Ames test with S typhimurium TA100 was used to compare mutagenic activities of NP in the presence and absence of S9 mix and to study changes in mutagenicity after exposing NP to sunlight. Potent, dose-related mutagenic effects and susceptibility to photodegradation are reported. (8 Refs)

31. SELECTIVE ACTIVATION OF SOME DIHYDRODIOLS OF SEVERAL POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENIC PRODUCTS BY PROSTAGLANDIN SYNTHETASE.

Guthrie J, Robertson IG, Zeiger E, Boyd JA, Eling TE
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Cancer Res; 42(5):1620-1623 1982

The ability of prostaglandin synthetase (PGS) to cooxidize benzo(a)pyrene, benzo(a)anthracene, chrysene, and several of their dihydrodiol derivatives to mutagenic products was tested with Salmonella typhimurium strain TA98 and TA100. The microsomal fraction of ram seminal vesicles, a known source of PGS, in the presence of the PGS substrate arachidonic acid, metabolized benzo(a)pyrene-7,8-dihydrodiol, benzo(a)anthracene-3,4-dihydrodiol, and chrysene-1,2-dihydrodiol to mutagenic products. This activity was inhibited by the PGS inhibitor indomethacin. Unlike the PGS system, however, a cytochrome P-450-reduced nicotinamide adenine dinucleotide phosphate-dependent system, present in an Aroclor 1254-induced rat liver 9,000 x g supernatant fraction, also activated the parent compounds [benzo(a)pyrene, benzo(a)anthracene, chrysene] and several other benzo(a)anthracene dihydrodiols (the 1,2-dihydrodiol, the 8,9-dihydrodiol, and the 10,11-dihydrodiol). The chrysene trans-3,4, trans-5,6, and cis-5,6 diols were not activated to mutagens by either system, Thus, the PGS system appears to be more selective than does the cytochrome P-450 system in the activation of polycyclic aromatic hydrocarbons to mutagenic products, activating only those dihydrodiols with adjacent double bonds in the bay region from which the bay-region diol-epoxides are formed. (Author abstract) (20 Refs)

32. ORIGIN OF MUTAGENICITY OF WELDING FUMES IN S. TYPHIMURIUM.

Stern RM, Thomsen E, Larsen H
Svejsecentralen, Glostrup, Denmark
Origin of Mutagenicity of Welding Fumes in S. typhimurium. Available from National Technical Information Service, Springfield, VA, as PB82-116245:, 62 pp., 1981.

The origin of mutagenicity in Salmonella typhimurium in response to exposure to welding fumes, a complex mixture of metallic oxides and other inorganic compounds, is studied through the quantitative use of the histidine revertant Salmonella microsome test of Ames. Dose-response experiments and factorial design studies independently show the mutagenic activity to be due to the presence of soluble Cr(VI). A rate of 65 plus or minus 15 revertants/plate/microgram Cr(VI) is found for all fumes produced by the metal inert gas welding of stainless steel: a significantly reduced rate is found for manual metal arc welding fumes. The presence of other metals in low oxidation states (eg Fe(O),Fe(II),Al(O)), results in a significant reduction of the Cr(VI), accompanied by a corresponding decrease of the absolute revertant rate per unit fume mass. (Author abstract)

33. APPLICATION OF THE SALMONELLA MUTAGENICITY ASSAY AND DETERMINATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN WORKPLACES EXPOSED TO PETROLEUM PITCH AND PETROLEUM COKE.

Monarca S, Pasquini R, Sforzolini GS, Viola V, Fagioli F
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Int Arch Occup Environ Health; 49(3/4):223-239 1982

The airborne particulates and the petroleum pitch (PP) and petroleum coke (PC) working materials in a carbon electrode factory were assayed for mutagenicity on Salmonella typhimurium TA98 and TA100 with or without S9 activation. The PP contained antanthrene (AA), benzo(k)fluoranthene (BkF), benzo(a)pyrene (BaP), fluoranthene (FA), and perylene (P); the PC contained BkF, BaP, FA, P, and benzo(b)fluoranthene. There was a dose-response mutagenicity relationship (DRMR) between PP extracts and TA98 with S9. The PC extracts were not mutagenic under any condition due to the low levels of the indicated polycyclic aromatic hydrocarbons. Airborne particulates from two distinct sites in the factory contained BkF, BaP, FA, and P, but not in the same ratios; one site also yielded AA. A DRMR was found for extracts from both sites under all conditions except TA100 without S9 at the site lacking AA. The demonstration of mutagenic activity in the airborne particulates not requiring S9 activation indicated the potential adverse effects of the thermal processing of the PP and PC. (41 Refs)

34. DETERMINATION OF MUTAGENIC POTENTIAL AND ORGANIC CONTAMINANTS OF GREAT LAKES DRINKING WATER.

Williams DT, Nestmann ER, LeBel GL, Benoit FM, Otson R
Bureau Chemical Hazards Environmental Health Directorate, Dept. Natl. Health and Welfare, Ottawa K1A OL2, Canada
Chemosphere; 11(3):263-276 1982

Summer and winter water samples taken directly from 12 treatment plants were passed through ion exchange resin filters to extract organic contaminants. Winter grab samples of raw and treated water were also taken at each plant at the same time and analyzed for volatile organics. The resin extracts were tested for mutagenicity with/without S9 activation against Salmonella typhimurium TA98 and TA100. The extracts were also analyzed for organochlorine and organophosphorus pesticides (OPP), trialkylphosphates and triarylphosphates (TAP), polychlorinated biphenyl (PCB), and polycyclic aromatic hydrocarbons (PAH). Extracts taken to dryness were more mutagenic than those left in solution. Mutagenicity was higher in the summer samples (11/12) than winter samples (7/12). Aggregate PAH was higher (11/12) in winter samples however; naphthalene, biphenyl, dibenzyl, fluorene, anthracene or phenanthrene, fluoroanthrene, pyrene, stilbene, fluorenone, and anthraquinone were found. The extracts contained (a) alpha-BHC and beta-BHC, both generally higher in winter, (b) no PCB or OPP, (c) TAP: ethyl, n-butyl, 2-chloroethyl, 1,3-dichloropropyl, butoxyethyl, phenyl, and cresyl, in seven instances only in summer samples. The grab samples contained bromodichloromethane, chlorodibromomethane, chloroform, toluene, m-xylene, and o-xylene. No relationships between relative mutagenicity and identified contaminants could be deduced. (19 Refs)

35. IDENTIFICATION OF NITROAROMATICS IN DIESEL EXHAUST PARTICULATE USING GAS CHROMATOGRAPHY/NEGATIVE ION CHEMICAL IONIZATION MASS SPECTROMETRY AND OTHER TECHNIQUES.

Newton DL, Erickson MD, Tomer KB, Pellizzari ED, Gentry P, Zweidinger RB
Dept. Environmental Sciences and Engineering, Univ. North Carolina, Chapel Hill, NC, 27514
Environ Sci Technol; 16(4):206-213 1982

Low pressure column chromatography fractions of a methylene chloride extract of diesel exhaust particulates were tested for mutagenicity on Salmonella typhimurium TA98 with and without metabolic activation. The fraction showing highest mutagenicity was assayed for nitropolycyclic aromatic hydrocarbon compounds, a class known to have mutagenic activity. Tentatively identified were nitroanthracene and/or nitrophenanthrene, nitropyrene and/or nitrofluoranthrene, nitrochrysene, methylnitropyrene, and methylnitroanthracene. A series of C1-C3 alkylnitroanthracene and/or alkylnitrophenanthrene compounds was identified in a nonmutagenic, adjacent chromatographic fraction. (25 Refs)

36. MUTAGENICITY OF AIRBORNE PARTICLES IN RELATION TO TRAFFIC AND AIR POLLUTION PARAMETERS.

Moller M, Alfheim I, Larssen S, Mikalsen A
Central Inst. for Industrial Res., P.O. Box 350, Blindern, Oslo 3, Norway
Environ Sci Technol; 16(4):221-225 1982

Air samples were taken day and night in a park and at 2 and 25 m heights in a nearby heavy traffic street. Extracts were tested for mutagenicity with and without S9 metabolic activation on Salmonella typhimurium TA98. S9 increased mutagenicity 2-3x in the 2 m street day samples. Day samples, park or street 25 m, were not influenced by S9, and had only 5-25% of the activity of day 2 m street samples. Depression of 2 m street activity at night corresponded to decrease in traffic. (26 Refs)

37. SELECTIVE DEACTIVATION OF ICR MUTAGENS AS RELATED TO THEIR DISTINCTIVE PULMONARY CARCINOGENICITY.

De Flora S, Morelli A, Zanacchi P, Bennicelli C, De Flora A
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Carcinogenesis; 3(2):187-194 1982

The mutagenicity patterns and the metabolic behavior of four structurally related ICR compounds were investigated using the Salmonella/microsome test. ICR 191 and ICR 170 reverted four his- strains (TA1537 greater than TA100 greater than TA98 and TA1538), while ICR 191-OH and ICR 170-OH reverted TA1537 only, with a narrow range of mutagenic activity. Although all the products tested were shown to contain a common mutagenic impurity, analysis of chemicals fractionated by hplc provided evidence that pure ICR 191-OH and ICR 170-OH also induce frameshift errors. The mutagenic activity of all the four ICR compounds, as well as of their common impurity, was decreased in the presence of S-9 mix containing rat liver S-9 fractions, a trend confirmed by hplc of ICR/S-9 mixtures. Despite the greater mutagenic potency in the absence of metabolic systems, ICR 191 was deactivated far more efficiently and rapidly than ICR 170 by a variety of mouse (liver greater than lung) and rat (liver greater than testis greater than kidney greater than lung greater than striated muscle greater than spleen) S-9 fractions. Mouse preparations were more effective than the corresponding rat preparations. Aroclor 1254 strongly stimulated the activity of the NADPH-requiring enzymes responsible for ICR deactivation. Hplc analyses ruled out interconversion among the four ICR compounds in the presence of liver S-9 fractions, while revealing the appearance of new distinct peaks for ICR 191, ICR 170 and ICR 170-OH. The selective metabolic deactivation of ICR compounds may be related to the findings of previous carcinogenicity studies which showed the induction of lung adenomas following iv but not ip administration of ICR 170. Conversely, ICR 191 and ICR 191-OH showed no activity even when administered iv. Since intercalation of ICR compounds into DNA is the molecular basis for both mutagenic and antitumor activities, their distinctive metabolic reactivity may be also responsible for the differential efficacy in pharmacological assays. (Author abstract) (27 Refs)

38. LEUKAEMOGENIC AND MUTAGENIC ACTIVITY OF THE BUTYROPHENON, 4-[4-(4-CHLOROPHENYL)-4-HYDROXY-1-PIPERIDINYL]-1-(4 FLUOROPHENYL)-1-BUTANONE (HALOPERIDOL).

Fey F, Wunderlich V, Teichmann B, Sydow G, Kohler S
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Carcinogenesis; 3(2):223-224 1982

Development of mainly monocytic-myeloid leukemias was observed in two strains of mice upon ip administration of 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4 fluorophenyl)-1-butanone (haloperidol), an antipsychotic drug. Haloperidol was also shown to be mutagenic in the Ames Salmonella test system. (Author abstract) (7 Refs)

39. METABOLISM, DISTRIBUTION, AND EXCRETION OF THE FLAME RETARDANT, TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (TRIS-BP) IN THE RAT: IDENTIFICATION OF MUTAGENIC AND NEPHROTOXIC METABOLITES.

Lynn RK, Garvie-Gould C, Wong K, Kennish JM
Dept. Pharmacology, Oregon Health Sciences Univ., Portland, OR, 97201
Toxicol Appl Pharmacol; 63(1):105-119 1982

Metabolism and distribution of tris(2,3-dibromopropyl) phosphate (Tris-BP) were followed in male Sprague-Dawley rats for 5 days after iv injection of 14C-Tris-BP. Approx 58% of radiolabel was excreted within 24 hr, and 86% by 5 days. At this time approx 9% of the dose remained in the body (95% recovery). Studies in several animals with exteriorized bile ducts showed that approx 34% of the dose was excreted in the bile at 24 hr, but that a minimum of 74% of this was reabsorbed. High pressure liquid chromatography demonstrated numerous radiolabeled components, of which bis(2,3-dibromopropyl) phosphate (Bis-BP) and 2,3-dibromopropanol (DBP) were identified. Tris-BP disappeared rapidly in tissues and was undetectable at 8 hr, but the half-life of Bis-BP was relatively long. Bis-BP concentrated in lung, muscle, fat, and especially blood, where it accounted for approx 90% of the radiolabel at 30 min and 8 hr. At 5 days the concentration of radiolabel was highest in the kidneys, 11x the av whole body concentration. This may be related to the polyuria induced by large doses of Tris-BP. In Ames mutagenicity testing on TA100 and TA1535, with microsomal activation, Tris-BP was most mutagenic, with Bis-BP and DBP approx equal at all concentrations except the highest (1,000 nanomole/plate), where Bis-BP was approx 80% more active. Previous work on Tris-BP is discussed and compared with these findings. (21 Refs)

40. SCREENING OF ANTIOXIDANTS AND OTHER COMPOUNDS FOR ANTIMUTAGENIC PROPERTIES TOWARDS BENZO[A]PYRENE-INDUCED MUTAGENICITY IN STRAIN TA98 OF SALMONELLA TYPHIMURIUM.

Calle LM, Sullivan PD
(c/o Sullivan) Dept. Chemistry, Ohio Univ., Athens, OH, 45701
Mutat Res; 101(2):99-114 1982

Mechanisms of antioxidant inhibition of carcinogenicity were studied by examining the effects of antioxidants on the oxidation of benzo[a]pyrene (BP) and its derivatives using the Salmonella typhimurium reversion test. The concentration ratio (compound/BP) was varied from 1-50 at a constant BP concentration of 8.2 nanomoles/ plate. Strong inhibitors were those which produced a greater than 25% inhibition of the mutagenicity of BP at concentrations no more than 5x the concentration of BP. According to this definition, disulfiram, phenothiazine, phenethyl isothiocyanate, phenyl isothiocyanate, and retinol were strong inhibitors. Weak inhibitors, producing greater than 25% inhibition at concentrations of no more than 50x the concentration of BP, included sodium selenite, polyvinylpyrrolidone, butylated hydroxytoluene (BHT), sodium diethyldisodium cyanate, and possibly butylated hydroxyanisole and ethoxyquin. Benzyl thiocyanate, ascorbic acid, glutathione, alpha-tocopherol, cysteamine, and sodium cyanate were not found to be inhibitors. Dose-response curves were obtained for the 17 most active compounds. Mechanisms of BP-induced mutagenicity are discussed. (67 Refs)

41. MUTAGENICITY OF CHLOROALKENE EPOXIDES IN BACTERIAL SYSTEMS.

Kline SA, McCoy EC, Rosenkranz HS, Van Duuren BL
Enzo Biochem, Inc., 325 Hudson St., New York, NY, 10013
Mutat Res; 101(2):115-125 1982

Epoxides of six chloro-olefins, cis-1-chloropropene oxide (1), trans-1-chloropropene oxide (2), cis-1,3-dichloropropene oxide (3), trans-1,3-dichloropropene oxide (4), trichloroethylene (5) and tetrachloroethylene oxide (6), were examined for mutagenicity in Salmonella typhimurium TA 1535 and Escherichia coli WP2 uvrA and for genotoxicity in E coli pol A-/pol A+ DNA repair assay in the absence of metabolic activation. In mutagenicity tests, the compounds (CPD) generally exhibited toxicity. However, at lower doses, concentration-dependent mutagenic responses in Salmonella TA1535 were obtained for all chemicals except for CPD 5. Similar results were obtained with E coli WP2 uvrA except that neither CPD 5 nor 6 were mutagenic. CPD 3 and 4 showed the highest specific mutagenicities. Both CPD 4 and its aqueous decomposition product exhibited dose-dependent mutagenicity, although the unhydrolyzed form was 2-3x more potent. In genotoxicity tests, CPD 1, 2, 3, and 4 were mutagenic for S typhimurium TA1535 and for E coli WP2 uvrA and differentially inhibited the E coli DNA repair-deficient strain. CPD 5 was not mutagenic for Salmonella and E coli WP2 uvrA, but exhibited DNA-modifying activity. CPD 6, while non-mutagenic for E coli WP2 uvrA, was mutagenic for Salmonella, and positive in the E coli pol A1-assay. CPD 3 and 4 exhibited the highest potencies in all the systems studied. The results indicated that alpha-chloroepoxides of biologically active halo-olefins are themselves biologically active in the absence of metabolic activation. (38 Refs)

42. GENOTOXICITY OF SAFROLE-RELATED CHEMICALS IN MICROBIAL TEST SYSTEMS.

Sekizawa J, Shibamoto T
Ogawa and Co. Ltd., 1-12-3 Niitaka, Yodogawa-Ku, Osaka, Japan
Mutat Res; 101(2):127-140 1982

Genotoxicities of saffrole, nine related compounds (anethole, cinnamaldehyde, cinnamyl alcohol, estragole, methyl eugenol, eugenol, isoeugenol, isosafrole, piperonal), five essential oils (anise oil, cassia oil, cinnamon bark oil, clove oil, fennel oil), and one oleoresin (pimenta oleoresin) were examined in the Bacillus subtilis DNA repair test (Rec assay) without S9 activation, in the Escherichia coli WP2 uvrA reversion test, and in a modified Ames test. No test compounds induced a significant increase in revertant numbers in either Salmonella tester strains or with E coli WP2 uvrA in the absence of S9. Anethole was the only compound that showed a significant increase in revertants in the presence of S9. A clear dose-dependent increase of induced mutation frequencies of TA100 cells was observed with anethole. All chemicals except anethole, estragole, and isosafrole were positive in the Rec assay without S9. The results are discussed in relation to the nature of the problems encountered with each test method. (20 Refs)

43. MUTAGENICITY OF SUBSTITUTED CARBAZOLES IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 101(2):141-150 1982

Mutagenic activities of several substituted carbazoles in Salmonella typhimurium TA1535, TA1537, TA1538, TA98, and TA100 were compared. Of all possible isomers of methylcarbazole, only 9-methylcarbazole was mutagenic when assayed in S typhimurium TA100 in the presence of S9. Other dimethylcarbazoles in which one of the methyl substituents was in the 9-position were similarly assayed for mutagenic activity; with the exception of 1,9-dimethylcarbazole, each of the compounds were mutagenic in TA100 with activation. The mutagenic potency of the dimethylcarbazoles was less than that of 9-methylcarbazole. All of the carbazole derivatives were inactive as mutagens in TA1535, TA1537, TA1538, and TA98, with or without S9 mix. Substitution at the 9-position of carbazole resulted in a loss of mutagenic activity. Metabolism studies performed with 9-methylcarbazole confirmed that 9-hydroxymethylcarbazole is a major metabolite and proximate mutagen. It was suggested that the mutagenicity of 9-hydroxymethylcarbazole is related to the release of formaldehyde, a hypothesis supported by the lack of mutagenic activity of 9-formylcarbazole and 9-acetylcarbazole. (17 Refs)

44. ON THE PROBLEM OF MICROBIAL MUTAGENESIS.

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Onkologie; 5(1):30-32,34-35 1982

Mutagenicity tests using microorganisms are the Salmonella-typhimurium test (Ames), the test with a polymerase A deficient Escherichia coli, the Saccharomyces cerevisiae D3 system and the Neurospora crassa test are reviewed. Differences in results of Ames-test may be due to differences preserving the tester strains, the choice of solvent and the dosage of the test compounds, last not least is the production of S-9. The polymerase A deficient Escherichia coli system seems easier to handle than the Saccharomyces cerevisiae- or Neurospora crassa-test. The metabolic activation with different forms of S-9 is needed in the Salmonella- and the Escherichia coli-system. Nevertheless it is not possible to decide if a substance is carcinogenic for human beings or animals with microbial mutagenicity tests only. (Author abstract) (20 Refs) (In GER)

45. SUBSTITUENT EFFECTS ON THE MUTAGENICITY OF PHENYL GLYCIDYL ETHERS IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 93(2):297-304 1982

The Ames test for mutagenicity was used with glycidyl phenyl ether, p-bromophenyl 2,3-epoxypropyl ether, 2,3-epoxypropyl p-methoxyphenyl ether, p-chlorophenyl 2,3-epoxypropyl ether, p-tert-butylphenyl 2,3-epoxypropyl ether, 2,3-epoxypropyl p-tolyl ether, and 1,2-epoxy-3-(p-nitrophenoxy)-propane. All seven compounds were mutagenic in both strains TA100 and TA1535, with the exception of the tert-butyl form, which was not active in TA1535. The Hammett sigma constants reported for the ionization of benzoic acid were compared to the mutagenicity of the phenyl glycidyl ethers. A reasonable correlation of mutagenicity in both strains was evident as compared to the Hammett sigma values for the para substituents. Mutagenicity generally increased with the strength of the electron-withdrawing substituent, particularly for the bromo, chloro, and nitro groups. (13 Refs)

46. STRUCTURE-MUTAGENICITY RELATIONSHIP IN ALPHA,BETA-UNSATURATED CARBONYLIC COMPOUNDS AND THEIR CORRESPONDING ALLYLIC ALCOHOLS.

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Mutat Res; 93(2):305-315 1982

The mutagenicities of 16 allylic alcohols and their carbonylic derivatives commonly used in industry were determined using the Ames test with Salmonella typhimurium TA100 in the modified suspension test of Rannug et al. Of the alcohols, allyl alcohol proved to be a potent mutagen (750 revertants/umole without S9 mix; 145 revertants/umole with S9); the next higher homolog and two isomers showed little or no mutagenic effect. Glycidol, the epoxide of allyl alcohol was distinctly mutagenic, but much less so than the non-epoxidized alcohol. Acrolein, crotonaldehyde, 2-methylacrolein, and methylvinyl ketone were strongly mutagenic without S9 mix; all but acrolein were also distinctly mutagenic with S9 mix. 2-cyclohexene-1-one was slightly mutagenic; cinnamylaldehyde and citral were not at all mutagenic according to the modified Ames test. In general mutagenicity was highest in the lowest members of homologous series, both of allylic alcohols and their corresponding unsaturated carbonyl compounds. There was a positive correlation between electrophilicity and direct mutagenicity. S9 mix did not increase mutagenicity in non-mutagenic compounds, but more or less inactivated the mutagenic compounds depending on their electrophilic properties. (23 Refs)

47. COMPARISON OF THE MUTAGENICITIES OF 4-AMINOBIPHENYL AND BENZIDINE IN THE SALMONELLA/MICROSOME, SALMONELLA/HEPATOCYTE AND HOST-MEDIATED ASSAYS.

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Mutat Res; 93(2):317-325 1982

The mutagenicity of two structurally related carcinogenic aryl amines, 4-aminobiphenyl (4-AB) and benzidine (BZ), which are subject to a complex in vivo metabolism, was studied by three different test methods. The Salmonella/microsome (S/m) assay was performed by the Ames method with strains TA1538 and TA100 of Salmonella typhimurium. In the Salmonella intrasanguineous assay, male Wistar rats (200 g) were injected in the lateral tail vein with 1 ml of saline suspension of S typhimurium, followed by ip injection of either 4-AB or BZ. Revertants in bacteria grown from liver suspensions were counted. The Salmonella/hepatocyte (S/h) assay involved counting of revertant colonies after plating from an incubation mixture containing rat liver hepatocytes, S typhimurium, and mutagen incubated at 37 C for 1 hr. The mutagenicity of the two compounds varied depending upon whether metabolic inactivation was carried on in vivo or by S9 mix in the Ames test. The results obtained for both compounds in the S/h assay resembled more closely those of the host-mediated assay than they did the results of the S/m assay. (16 Refs)

48. POTENT MUTAGENIC IMPURITIES IN A COMMERCIAL SAMPLE OF 3-NITRO-9-FLUORENONE.

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Cancer Lett; 15(3):209-214 1982

Potent mutagenic impurities were detected in a commercial sample of 3-nitro-9-fluorenone (NFN); characterization of these impurities by high pressure liquid chromatography (HPLC) and high-resolution mass spectrometry (HRMS) is reported. Several peaks were noted in the HPLC chromatogram of NFN, indicating that the impurities were present. When tested for mutagenicity in the Ames Salmonella assay, Fractions II, III, IV, and V were active. Fraction II accounted for 88% of the mass but its specific activity was at least 20x less than that of Fractions III and V. HRMS revealed the accurate masses of these fractions. Fraction II was a mononitrofluorenone. Fraction III and V yielded molecular ion peaks and fragmentation patterns of structures corresponding to a dinitrofluorenone and an acetamidomononitrofluorenone. Two commercially available standards, 2,7-dinitro-9-fluorenone (DNFN) and 2-acetamido-3-nitro-9-fluorenone (ANFN), were used for comparing with the unknown fractions. The HPLC retention time of DNFN was practically the same as that of Fraction III and that of ANFN was close to that of Fraction V. The mutagenic activities of DNFN and ANFN were also similar to the activities of the corresponding Fractions III and V: 0.10-0.22 ug of each chemical yielded 1,000 TA98 revertants in the linear region of the does-response correlation. Fraction IV yielded a compound with an accurate mass and fragmentation pattern similar to xanthone (XT). XT was not mutagenic in the TA98 assay when tested at doses up to 10 ug/plate. (14 Refs)

49. ESTABLISHMENT OF STOCHASTIC SIGNIFICANCE IN AMES TESTS AND ITS RELEVANCE TO GENETICAL SIGNIFICANCE.

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Mutat Res; 104(1-3):25-28 1982

Multiples of spontaneous frequency (usually 2-4 fold) have been the generally accepted criteria for significance in mutagenicity testing using the Ames' test with Salmonella. These criteria are, however, inappropriate to the measurement of significance for the low level of responses which occur periodically during the routine screening of compounds. Stochastic significance alone, is insufficient as a measure of genetic (biological) significance. For genetical significance, data must be stochastically significant (determined non-parametrically on consistency of result) and they must show a sufficiently large increase over the control to be considered quantitatively significant. (12 Refs)

50. PLATE ASSAY FOR CHEMICAL- AND RADIATION-INDUCED MUTAGENESIS OF CAN1 IN YEAST AS A FUNCTION OF POST-TREATMENT DNA REPLICATION: THE EFFECT OF RAD6-1.

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Mutat Res; 93(2):339-352 1982

In order to monitor the yield of induced can1 mutants of Saccharomyces cerevisiae before, during, and after the first round of post-treatment DNA replication, a method was developed. Mutagen-treated stationary-phase cells were permitted to divide on synthetic agar growth medium for varying time periods before mutant selection with top agar medium containing L-canavanine (CAN). With the CAN overlay method the initial number of viable cells plated remains constant so that an increased mutant yield with time should reflect a component of mutagenic potential requiring DNA replication. The predominant component of UV- and hydrazine (HZ)-induced CAN1 mutagenesis appears pre-replicative and replicative (or post-replicative), respectively. The advantage of the overlay method is that it permits observation of the kinetics of induced mutation at CAN1 in relation to post-treatment DNA replication in the absence of exogenous inhibitory substances. The rad6-1 allele significantly reduces frequencies of both UV- and HZ-induced mutagenesis at CAN1; experiments involving both liquid and agar post-treatment showed that the rad6-1 defect in UV mutagenesis cannot be alleviated by allowing DNA replication. (14 Refs)

CYTOGENETIC TESTS

51. 5-BROMODEOXYURIDINE TABLETS WITH IMPROVED DEPOT EFFECT FOR ANALYSIS IN VIVO OF SISTER-CHROMATID EXCHANGES IN BONE-MARROW AND SPERMATOGONIAL CELLS.

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Mutat Res; 97(2):117-129 1982

Uncoated and agar-coated tablets of 5-bromodeoxyuridine (BrdU; 50 mg) were implanted sc into NMRI mice. Compared to the uncoated tablets, agar-coated tablets provided a slower, more uniform delivery of BrdU. The slow dissolution rate of the agar-coated tablets permitted a reduction of the BrdU doses for assays of sister chromatid exchanges (SCE) in the bone marrow, thereby reducing undesired effects of high BrdU doses on the baseline SCE frequency as well as on cellular replication and proliferation. The agar-coated tablets could also be used to study SCE figures in the spermatogonia. (31 Refs)

52. A COMPARISON OF INDUCED SISTER CHROMATID EXCHANGE LEVELS IN CHINESE HAMSTER OVARY CELLS AND CULTURED HUMAN LYMPHOCYTES.

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Environ Mutagen; 4(1):65-71 1982

The effects of six DNA damaging agents on the induced sister chromatid exchange (SCE) rate were compared in peripheral blood lymphocytes from healthy human subjects and Chinese hamster ovary (CHO) cells. Both types of cells were exposed to two cycles of each agent. Differential staining of SCE was by a slight modification of the method of Perry and Wolf. Dunnett's test for multiple comparison was used to determine which treatment groups differed from controls. Significantly increased SCE levels were observed in CHO cells after 5-bromodeoxyuridine (50 ug/ml), proflavine (0.2 and 0.5 ug/ml), bleomycin (2.0-6.0 ug/ml), vincristine (0.05-1.00 ug/ml), and 3H-uridine (0.37 and 3.70 kBq/ml). SCE levels of human lymphocytes were only increased by 5-bromodeoxyuridine, proflavine, and the highest dose of 3H-uridine. Colcemid did not increase SCE in either cell system. It is suggested that SCE analysis in response to mutagens and carcinogens should be based on more than one cell type. (26 Refs)

53. SISTER-CHROMATID EXCHANGE INDUCTION BY CIS-PLATINUM/ADRIAMYCIN CANCER CHEMOTHERAPY.

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Mutat Res; 104(1-3):131-136 1982

Induction of sister-chromatid exchanges (SCE) by chemotherapy with cis-platinum (cis-DDP) and adriamycin (ADM) was studied in five patients (3 men and 2 women, 55-72 yr old) with advanced metastatic cancer. Tumors included adenocarcinoma of the ovary (Stage III), carcinosarcoma of the endometrium, transitional cell carcinoma of the bladder (Stage IV, 2 cases), and epidermoid cancer of the head and neck. All patients had undergone previous chemotherapy at varying intervals prior to the study. SCE and chromosomal aberrations (CA) were measured in cultures of peripheral lymphocytes obtained 1 mo after a course of chemotherapy or 5 hr after iv infusion of cis-DDP (100-110 mg) and ADM (100-110 mg). Twenty-two patients with solid tumors sampled before therapy served as controls. Cells were incubated for 72 hr. CA grade included chromatid and isochromatid breaks, acentric fragments, rings, dicentrics, and exchange figures. The frequency of SCE was similar in untreated patients (7.57 +-0.83 SCE/cell) and noncancer controls (6.92 +-0.80 SCE/cell). Pretreatment frequencies were higher (10.05 +-2.54 SCE/cell) in the test patients, probably due to effects of prior chemotherapy. Cultures of cells collected 5 hr after treatment showed 18.97 +-1.97 SCE/cell. Two test patients had normal SCE values 1 mo after prior chemotherapy. CA were found in 7.0 +-5.2% of cells. SCE provided a better index of mutagenic exposure than CA. Results indicate short-term mutagenic effects of chemotherapy with cis-DDP and ADM. (9 Refs)

54. INDUCIBILITY OF SISTER-CHROMATID EXCHANGES BY HEAVY-METAL IONS.

Ohno H, Hanaoka F, Yamada M
Dept. Physiological Chemistry, Faculty Pharmacological Sciences, Univ. Tokyo, Hongo, Tokyo 113, Japan
Mutat Res; 104(1-3):141-145 1982

Induction of sister-chromatid exchanges (SCE) by heavy metal ions was studied in Don Chinese hamster (DCH) cells in vitro. In each test 4 x 10(4) cells were incubated for 72 hr with 1 ml growth medium and a particular concentration of metallic compound. Cultures were exposed to 5-bromo-2'-deoxyuridine (BUdR) for two cell cycles (28 hr). Metal ions tested included Ti+++, Cr+++, Cr++++++, Fe++, Fe+++, Ni++, As+++, As+++++, Se++, Cd++, Sn++, and Hg++. Metallic compounds were dissolved in dimethyl sulfoxide. Median tissue culture inhibition doses (TCID50) were calculated by microscopic examination of fixed, stained cells. Rates of SCE were calculated for the TCID50 of each test ion. Spontaneous SCE occurred in untreated control cells at a rate of 3.90 +-0.82 SCE/metaphase. Any result greater than 5.4 SCE was considered to be a significant increase. Significant increases were produced by Cr+++, Cr++++++, Ni++, As+++, and As+++++. Cr++++++ produced a greater increase in SCE than did Cr+++. As+++ produced a greater increase in SCE than did As+++++. Although Se++ is a suspected carcinogen, increased SCE were not produced at TCID50. (17 Refs)

55. EXTRAORDINARILY HIGH MICRONUCLEUS FREQUENCY INDUCED BY X-RAYS IN A SPECIAL CLONE OF TRADESCANTIA REFLEXA.

Ma TH, Fang T, Ho J, Chen D, Zhou R, Lin G, Dai J, Li J
Western Illinois Univ., Macomb, IL
Mutat Res; 104(1-3):101-103 1982

X-ray dosages were recalibrated with an ion chamber dosimeter and two series of Tradescantia-micronucleus (Trad-MCN) bioassays were performed to compare the radiosensitivities of Tradescantia paludosa and Tradescantia reflexa. The MCN frequencies of the treated and control groups in the repeated experiments were relatively consistent in both species and proportional to the dosages applied. The averages of the two series of experimental results indicated roughly 1-4x greater MCN frequency in T reflexa than in T paludosa. Implications of discovery of the T reflexa strain for mutagenesis studies are discussed. (4 Refs)

56. NOTE ON THE UTILITY OF THE ST MUS302 TEST FOR CHROMOSOME LOSS IN A BLIND TEST OF AN ENVIRONMENTAL COMPOUND FOR CHROMOSOME BREAKAGE IN DROSOPHILA.

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Mutat Res; 104(1-3):117-119 1982

A compound identified as beta-propiolactone (BP) was tested for chromosome breakage in the heritable translocation test, using Drosophila females from the repair-deficient strain st mus302. Results of sex-linked lethal tests for point mutations and heritable translocation tests to detect translocations between chromosomes 2 and 3 and between the Y chromosome and chromosome 2 and/or 3 were positive. Xc2, y f/BSYy+ males were treated with 7.5 mg/ml BP and mated as follows: in Experiment I, to mei-9a and st mus 302 females and in Experiment II, to repair-proficient and st mus302 females. With mei-9a females, significant increases in both complete and partial chromosome loss were observed; the frequency of total loss was 2.2%, greater than the induced translocation cited for other tests. With st mus/302, a substantially stronger effect was found, the total loss reaching 13.8%. In Experiment II, results with repair-proficient females failed to indicate a significant increase in chromosome loss, whereas with st mus302 total loss was 10.1%. (7 Refs)

57. INDUCTION OF NUCLEAR ANOMALIES (MICRONUCLEI) IN THE PERIPHERAL BLOOD ERYTHROCYTES OF THE EASTERN MUDMINNOW UMBRA PYGMAEA BY ETHYL METHANESULPHONATE.

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Mutat Res; 104(1-3):147-152 1982

The suitability of a micronucleus test with fish as a convenient and rapid test for detecting genotoxic compounds in the aquatic environment was examined using the eastern mudminnow Umbra pygmaea. The test agent, the direct-acting mutagen ethyl methanesulfonate (EMS) was administered in doses of 0-200 mg/liter over 3 wk or in 8-40 mg/liter over 6 wk. The incidence of nuclear anomalies in peripheral RBC of the mudminnows was determined. EMS caused damage to nuclei; in addition to characteristic micronuclear abnormalities, irregular Feulgen-positive structures and nuclear structural irregularities were observed. The effect of EMS was dose-dependent and very probably time-dependent. The results indicated that EMS, which is representative of a large class of alkylating agents and positive in a variety of genotoxicity tests, caused damage to the RBC nucleus of the fish U pygmaea. The test with fish RBC may be used as an alternative to the chromosome aberration test. (8 Refs)

58. SHORT-TERM TESTS FOR TRANSPLACENTALLY ACTIVE CARCINOGENS. SENSITIVITY OF THE TRANSPLACENTAL MICRONUCLEUS TEST TO DIETHYLNITROSAMINE.

Cole RJ, Taylor N, Cole J, Henderson L, Arlett CF
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Mutat Res; 104(1-3):165-171 1982

Dose-dependent clastogenic effects of diethylnitrosamine (DEN) in utero were examined using the transplacental micronucleus test. Random-bred albino mice were mated and treated with DEN ip. Frequencies of polychromatic RBC containing micronuclei were determined in preparations of fetal liver and neonatal peripheral blood. The youngest animals investigated were exposed to DEN in utero during days 15-16 of gestation. A small but significant increase in frequency of micronucleated polychromatic RBC (MNPCE) was detectable in fetal liver 36 hr after treatment. A high level of significance was obtained when exposure was initiated during day 17 of gestation. No increases in frequency of MNPCE were observed in maternal bone marrow. Polychromatic RBC derived from fetal liver during the last day of gestation persisted in the circulation of neonatal animals. Therefore, the frequency of

MNPCE in smears of peripheral blood can be used to measure clastogenic effects when the metabolic capacity of the prenatal liver is fully expressed. Pregnant animals were treated late on day 17 of gestation and blood smears were prepared from newborn animals 45 hr after beginning exposure. Dose-related increases in frequencies of MNPCE in neonatal mice after in utero exposure were obtained. Variation in response to DEN between members of litters and between litters was greater than observed with other chemicals, suggesting that onset of the ability to metabolize DEN is variable. (28 Refs)

59. HERITABLE TRANSLOCATION TEST IN MICE WITH TRIETHYLENEMELAMINE (TEM) AND ERGOTAMINE.

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Preclinical Res., Toxicology, Sandoz Ltd., Basel, Switzerland
Mutat Res; 104(1-3):177-182 1982

The ability of ergotamine tartrate (ET) to induce transmissible chromosome aberrations was determined in a heritable translocation test. Triethylenemelamine (TEM) was used as a positive control. ET (125 mg/kg ip) and TEM (0.2 mg/kg ip) were administered to randomly bred albino male CD-1 mice. The males were mated to untreated virgin females on days 8-14 post-treatment. All F1 males resulting from conceptions during this interval (220 males in the ET group, 144 in the TEM group, and 233 controls from untreated fathers) underwent fertility tests. Fertility patterns in the control and ET groups were similar, whereas in the TEM group, a slight reduction in the number of total and living implantations and an increase in dead implantations occurred. Of 233 control males, 229 were fertile, 3 were sterile, and one was 'questionable.' No partially sterile males were identified. In the ET group, 1 male was sterile and another was classified as questionable; 118 males were highly fertile. In the TEM group, 22/144, 9/144, and 8/144 males were classified as partially sterile, sterile, and questionable, respectively. None of the males in the control or ET groups were translocation carriers according to cytological examination. In the TEM group, 22/22 partially sterile, 3/9 sterile, and 5/8 questionable males were proven cytologically to be translocation carriers. The six non-cytologically confirmed steriles had no diakinesis-metaphase I cells. The results suggested that the most reliable methodology for detecting heritable translocations in CD-1 mice is the combination of conventional methodology in fertility testing with cytological analysis of all sterile, partially sterile, and questionable males. (13 Refs)

60. CYTOGENETIC ACTIVITIES OF 3 SULPHONAMIDES.

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Mutat Res; 104(1-3):95-100 1982

Cytogenetic effects of three sulfonamides were tested in Allium cepa (cv Giza). Bulbs with growing root tips were exposed to sulfadiazine (2-p-aminobenzene sulfonamide pyrimidine), sulfadimidine (2-p-aminobenzene sulfonamide 5-p-aminomethyl pyrimidine), or sulfaphenazole (5-p-aminobenzene sulfonamide-1-phenyl pyrazole) at concentrations of 0.02, 0.2, 1.0, or 2.0 mg/ml for 4, 24, or 48 hr. Cytological effects were studied by means of the Feulgen squash technique. Compared with controls, mitotic indices (MI) were increased by all three test compounds after 4-hr exposures and reduced after 24-and 48-hr exposures. Reduction in MI were concentration-dependent. Increasing exposure time from 24 to 48 hr produced only slight additional reduction in MI. MI were reduced to less than 50% of control values by concentrations of 1 or 2 mg/ml. All three test compounds produced high frequencies of mitotic and chromosomal abnormalities (C-metaphases, multipolar mitoses, polyploidy, chromosome lagging, stickiness, bridges, and breakage) after 4-hr exposures. The frequency of abnormalities was decreased after 24-hr exposures and increased relative to 24-hr exposures by 48-hr exposures. Wide variations were observed among roots undergoing the same treatment. Mitotic abnormalities were more common after 4-hr exposures, while chromosomal abnormalities were more common after 24-or 48-hr exposures. Results suggest possible mutagenic effects in humans. (18 Refs)

61. SCE INDUCTION IN HUMAN LYMPHOCYTES BY COMBINED TREATMENT WITH ANILINE AND NORHARMAN.

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Dept. Biology, Keio Univ., Yokohama 223, Japan
Mutat Res; 101(2):165-172 1982

The ability of aniline (AL) and norharman (NH) to induce an increase in the number of sister chromatid exchanges (SCE) was examined in peripheral blood lymphocytes from normal healthy males. After a 24 hr exposure of lymphocytes to AL (2 x 10(-3) and 10(-2) M) a very slight increase in SCE frequency was observed. After 48-hr AN treatments (10(-2) M), few if any cells were found at second mitosis. At 10(-3) and 10(-4) M AN concentrations, an increase in SCE was not apparent. Treatment with the AN metabolite p-aminophenol (10(-4) M) increased the yield of SCE. Addition of S9 mix did not result in increased SCE. Treatment of lymphocytes with AN plus NH in the presence of S9 mix increased SCE frequencies. NH plus S9 also induced an increase in SCE. The incidence of SCE decreased with increasing concentrations of AN in treatments with AN, NH, and S9 combined. Thus, AN seemed to counteract the SCE-inducing activity of activated NH. The frequency of NH-induced SCE was dose-dependent and increased with increasing concentrations of S9. Simultaneous application of NH and AN for 48 hr did not affect the NH-induced SCE frequencies. The results indicated that the addition of NH, which enhances the sensitivity of the Salmonella/microsome test, does not produce an enhancement of the sensitivity of the SCE test. (13 Refs)

62. MUTAGENIC EVALUATION OF MORPHINE SULPHATE AND PETHIDINE HYDROCHLORIDE IN MICE BY THE MICRONUCLEUS TEST.

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Indian J Med Res; 75:112-117 1982

Mutagenicity of morphine sulfate (MS) and pethidine hydrochloride (PH) was evaluated in vivo by the micronucleus test in mice. The animals were treated ip with various doses of either MS or PH twice with an interval of 24 hr. At 6 hr after the second treatment they were killed and bone marrow smears were prepared. Polychromatic and normochromatic erythrocytes and nucleated cells were examined for the occurrence of micronuclei. Distilled water treated individuals served the purpose of control. The erythrocytes showed significant increase in the incidence of micronuclei at all the dose levels tested for both the drugs, which clearly indicated chromosome breaking ability of the narcotics. Comparative analysis of the data for the two drugs exhibited slightly higher effectiveness of morphine in producing micronuclei. Importance was not attached to the incidence of micronuclei in the nucleated cells because of some doubt in scoring. The chromosome breaking activity of the narcotics and their probable modes of action have been discussed. (Author abstract) (21 Refs)

63. THE NEUROBLAST OF THE GRASSHOPPER EMBRYO AS A NEW MUTAGEN TEST SYSTEM. I. IN VITRO RADIOSENSITIVITY.

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Mutat Res; 93(2):401-408 1982

Embryo neuroblasts of the grasshopper (Chortophaga viridifasciata De Geer) at 14 days of development (25 C) were prepared by an aceto-carmine squash method and examined for chromosome breakage induced by 8, 16, or 32 R of x-irradiation. Mitotic activity in unirradiated embryos was similar up to about 12-20 hr whether grown in vitro or in vivo. Chromsome aberration frequencies of in embryos cultured in vivo or in vitro after a 6-8 hr recovery period following irradiation were dose-dependent and not significantly different for the two growth modes. The neuroblast of grasshopper embryo offers several advantages over other methods for testing chemical clastogens, including radiosensitivity, extremely low frequency of spontaneous breaks, easy identification of clastogen-induced fragments, a short cell cycle, ease of slide preparation, large number of cells per 14-day embryo, and ease of maintenance of an animal colony. (14 Refs)

64. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

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Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

65. CLASTOGENIC ACTIVITY OF BILE ACIDS AND ORGANIC ACID FRACTIONS OF HUMAN FECES.

Barnes WS, Powrie WD
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Cancer Lett; 15(3):317-327 1982

Clastogenic activity in bile acids and in the acid fractions (AF) of saponified chloroform-methanol extracts (CME) from human fecal matter (FM) is reported. AF of saponified CME from four human donors were studied. With AF of FM from subjects A and B, frequencies of aberrant metaphases and exchanges were considerably higher than those for the control. The C and D AC also brought about a slight elevation in aberrations. The addition of S9 mix did not enhance the clastogenic activities of AF. With hexane extracts, no detectable increase in frequency of chromosome aberrations above control values were observed, either with or without the addition of S9 mix. When five of the major bile acids were assayed, cholic acid induced a slight increase in aberration frequency and ursodeoxycholic acid (UDCA) a much larger one. Addition of S9 enhanced the increase, but the presence of S9 was not a necessary condition for the demonstration of clastogenic activity. S9 also decreased the concentration of bile acid necessary to produce chromosome damage. Experiments using the standard S9 mix containing all cofactors, the standard S9 mix without NADPH, and an S9 mix with all cofactors in which the microsomal protein had been coagulated by heating to 80 C for 3 min, were performed. UDCA induced a large number of exchanges in conjunction with all S9 mixes, and while small differences attributable to treatment exist, the activity of NADPH-requiring mixed function oxidases is not necessary. The heat-treated S9 mix increased the toxicity and the frequency of exchanges relative to control. (31 Refs)

66. HYPOTONIC DESTRUCTION UNCOVERS CHROMOSOMAL ABERRATION.

Schroder J, Grunewald B, Struck L
Institut fur Rechtsmedizin der Universitat, D-2000 Hamburg, W. Germany
Naturwissenschaften; 69(3):150 1982

Nuclei with appendages resembling drumsticks or micronuclei were discovered following hypotonic treatment of leukemic WBC in mature and immature myeloid cells from 3/5 patients with acute myeloid leukemia. The results suggested that the appendage may represent a supernumerary chromosome inactivated during interphase. Screening for nuclei with appendages following hypotonic treatment may possibly be useful in determining cell lines with certain types of chromosomal changes. (4 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

67. CRITICAL APPRAISAL OF THE 'MOUSE TESTICULAR DNA-SYNTHESIS INHIBITION TEST' FOR THE DETECTION OF MUTAGENS AND CARCINOGENS.

Donatsch P, Gurtler J, Matter BE
Preclinical Res. Dept., Toxicology Unit, Sandoz Ltd., Basel, Switzerland
Mutat Res; 92(1/2):265-273 1982

The inhibition of testicular DNA synthesis (DSI test) in mice, proposed as a short-term in vivo assay for potential environmental mutagens and carcinogens, is examined. Male CD-1 mice were given single large doses of 1 of 10 chemicals whose mutagenic activities had been identified by other methods. The effects of reduced testicular temperature (caused by immobilization in a water bath at low temperatures) on testicular DNA synthesis were also studied. Hypothermia was observed after treatment with 6/6 nonmutagens and 3/4 known mutagens, and was associated with inhibition of testicular DNA synthesis. Testicular DNA synthesis inhibition caused by some of the test agents could be reduced under isothermal conditions. The DSI test is not thought to be a reliable means for detecting potential environmental mutagens and carcinogens. (6 Refs)

68. THE HELA DNA-SYNTHESIS INHIBITION TEST AS A RAPID SCREEN FOR MUTAGENIC CARCINOGENS.

Painter RB, Howard R
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Mutat Res; 92(1/2):427-437 1982

DNA synthesis inhibition (DSI) in HeLa and other mammalian cells was used for rapid detection of relatively strong mutagenic carcinogens. Of 90 agents tested for DSI in HeLa cells, the weaker DNA-damaging agents generally gave positive results only at high doses (1 milliM or greater) and very weak agents (eg, saccharin) gave negative results. One false positive result (cytochalasin B) was observed, with an atypical dose-response curve. The DSI test seems unsuitable for complex mixtures, probably because the DSI activity of a DNA-damaging agent may be masked by the actions of agents without DNA-damaging activity but which inhibit DNA synthesis by other means. (27 Refs)

69. VALIDATION OF A DNA-REPAIR SYNTHESIS ASSAY ON POOLS OF FRESH AND FROZEN-THAWED LYMPHOCYTES.

Capelli E, Stefanini M, Giulotto E, Nuzzo F
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Mutat Res; 104(1-3):187-191 1982

The possibility of measuring [3H]thymidine incorporation (HTI) stimulated by various treatments was studied in human lymphocyte pools, both fresh and thawed, after storage in liquid nitrogen. For each experiment cells obtained from 4-6 blood samples were mixed in equal proportions prior to exposure. Reagent grade purity chemicals and ranges tested were ethyl methanesulfonate (EMS) 5-20 milliM (mM), methyl methanesulfonate (MMS) 0.5-4 mM, epichlorhydrin (ECCH) 10(-4)-10(2) mM, mitomycin C (MC) 10(-6)-10(2) mM, hycanthone (HY) 10(-2)-2 mM, and cycloheximide (CHX) 3.5 x 10(-3)-3.5 x 10(-2) mM. Repair synthesis was expressed as the difference between HTI values in the presence of hydroxyurea (HU) in treated and untreated cells. CHX reduced HTI without any stimulation of repair. MMS, EMS, and ECCH induced repair synthesis at various concentrations, irrespective of the degree of inhibition of duplicative synthesis. HY inhibited DNA synthesis and induced a slight HTI increase only at 0.1 mM. MC reduced DNA synthesis at the highest concentration assayed and did not significantly increase the HTI rate in the presence of HU. Mean values of repair synthesis obtained with agents in different experiments are presented. The mean cell viability after thawing was 97.2% and decreased with incubation time (64.4% after 24 hr at 37 C). Repair synthesis activity was always present. HTI values in irradiated cells, both in the presence and absence of HU were always higher than in control cells. Results indicate that pools human lymphocytes can be used as an alternative to heteroploid cell lines and diploid fibroblasts in DNA-repair assays. (13 Refs)

70. NONDETECTION OF O(6)-METHYLGUANINE IN RAT DNA FOLLOWING IN VIVO TREATMENT WITH LARGE DOSES OF CIMETIDINE ALONE OR IN COMBINATION WITH SODIUM NITRITE.

Kyrtopoulos SA, Hadjiloucas E, Vrotsou B
Natl. Hellenic Res. Foundation, Biological Res. Center, 48 Vassileos Constantinou Ave., Athens, T.T. 501/1, Greece
Cancer Res; 42(5):1962-1966 1982

Cimetidine was administered by stomach tube to rats at 70 or 700 mg/kg, doses corresponding to 5 or 50 times, respectively, the typical daily dose of individuals on cimetidine treatment. In some cases, cimetidine (70 mg/kg) was administered in combination with a two-fold molar excess of sodium nitrite. This treatment was carried out up to six times over a 3-day period, the pH of the rat stomach being maintained at 2.3 to 3.0 for about 1 hr after each treatment. The DNA of the stomach, liver, and intestines (large and small pooled together) were isolated 6 hr after cessation of treatment and analyzed for the presence of O6-methylguanine using a sensitive and specific radioimmunoassay. No evidence could be obtained for the presence of this methylated base in any of the DNA samples examined, the limit of detection being 3 umol O6-methylguanine per mol guanine. We suggest that the observed lack of DNA methylation may be primarily due to the slow rate of nitrosation of cimetidine in combination with its rapid absorption into the blood stream. (Author abstract) (38 Refs)

71. SCINTILLOMETRIC DETERMINATION OF DNA REPAIR IN HUMAN CELL LINES: A CRITICAL APPRAISAL.

Bianchi V, Nuzzo F, Abbondandolo A, Bonatti S, Capelli E, Giorio R, Giulotto E, Mazzaccaro A, Stefanini M, Zaccaro L, Zantedeschi A, Levis AG
Istituto di Biologia Animale, Universita di Padova, Via Loredan 10, 35100 Padova, Italy
Mutat Res; 93(2):447-463 1982

The ability of a UV- and x-irradiation and a variety of chemical agents to stimulate DNA repair synthesis in human heteroploid EUE cell cultures was tested by a simplified (3H)thymidine-incorporation scintillometric procedure, with the use of hydroxyurea (HU) to suppress DNA replicative synthesis. The percentage residual DNA synthesis, the absolute increase in DNA radioactivity, as the ratio treated/control, the relative increase in DNA radioactivity, which is an index of DNA repair stimulation, and unscheduled DNA synthesis as measured by autoradiography were determined. The agents used fell into four groups: inhibitors of DNA replication, with evident absolute and relative increases in radioactivity, inhibitors of replication with relative but not absolute increases in radioactivity, compounds not altering any observed parameter, and inhibitors of replication giving negative absolute and relative increases in DNA radioactivity. The procedure described is an improved approach to screening chemicals able to induce DNA repair in mammalian cell cultures, which avoids time-consuming autoradiographic analysis when the scintillometric parameters are definitely positive or negative. (45 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

72. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

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Dept. Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK+/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (2.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

73. EFFECT OF MICROSOMAL CYTOCHROME P-450 ISOENZYME INDUCTION ON THE MUTAGENIC ACTIVATION OF 2-AMINOANTHRACENE.

Norman RL, Muller-Eberhard U, Johnson EF
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Cancer Res; 42(5):1722-1726 1982

Two rabbit microsomal cytochrome P-450 isozymes, Forms 4 and 6, which are differentially induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the liver in an age-dependent fashion, catalyze the activation of 2-aminoanthracene to a mutagen in the Ames Salmonella mutagenesis assay. We have shown previously that in the presence of saturating concentrations of 2-aminoanthracene, Form 4 is 15-fold more active than Form 6 in the activation of this mutagen. Similar differences in the activation of 2-aminoanthracene are observed between liver microsomes isolated from TCDD-treated adult rabbits, in which Form 4 predominates, and microsomes from rabbit neonates exposed transplacentally to TCDD prior to birth, in which Form 6 predominates. However, when the extent of mutagenesis is limited by the amount of 2-aminoanthracene and is independent of the rate of activation, the number of revertants produced is similar for microsomes isolated from either newborn or adult TCDD-treated rabbits. Under these conditions, the extent of mutagenesis obtained for a given amount of 2-aminoanthracene will depend on the balance between activation and competing reaction pathways leading to detoxication. Thus, differences in the rate of activation between adult and newborn microsomes are probably offset by similar differences in the rates of competing pathways of metabolism. This is consistent with the finding that the overall rate of 2-aminoanthracene metabolism by the adult microsomes is greater than that of the neonate. In order for the extent of mutagenesis to be independent of rate, the half-life of 2-aminoanthracene was seen to be less than approx 12 min. (Author abstract) (15 Refs)

74. THE USE OF PRIMARY RAT HEPATOCYTES TO ACHIEVE METABOLIC ACTIVATION OF PROMUTAGENS IN THE CHINESE HAMSTER OVARY/ HYPOXANTHINE-GUANINE PHOSPHORIBOSYL TRANSFERASE MUTATIONAL ASSAY.

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Environ Mutagen; 4(1):55-64 1982

Details are presented of a method used to evaluate the use of primary rat hepatocyte-mediated mutagenicity with the use of the Chinese hamster ovary (CHO)/hypoxanthine-guanine phosphoribosyl transferase mutational assay. Aflatoxin B1 (AFB1), 7,12-dimethylbenz(a)anthracene (DMBA), and benzo(a)pyrene produced increases in mutant fractions of treated CHO cells as a function of concentration. The time required for optimum expression of mutant phenotype was approx 8 days after exposure to DMBA and AFB1. (35 Refs)

COMPARATIVE TEST RESULTS

75. COMPARISON OF THE GENOTOXIC ACTIVITIES OF EXTRACTS FROM AMBIENT AND FOREST FIRE POLLUTED AIR.

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Graduate Center for Toxicology, Univ. Kentucky, 202 Medical Center Annex 5, Lexington, KY, 40536

Environ Mutagen; 4(1):37-43 1982

The genotoxicity of soluble, organic extracts of airborne organic particles was tested with use of the Salmonella reversion assay and the sister chromatid exchange (SCE) assay in cultured human lymphocytes. Airborne particles were collected in high volume air samplers in a non-industrial urban area under normal conditions (ambient) and during a period when dense smoke from a forest fire was carried by the wind into the area of the collectors. Salmonella strains TA98 and TA100 were used with and without Aroclor-induced rat liver S9 homogenate. While each sample caused increases in revertants in the Ames assay and increased incidence of SCE/cell, on the basis of the volume of air sampled, smoke-filled air induced 12-14x more bacterial reversions in TA100 and 16-38x more in TA98 than ambient (non-smoky) air. On a volume basis, 'smoky' air induced 43x more SCE in human lymphocytes than did ambient air. On the basis of extract weight, the 'smoky' air extract induced more SCE in human lymphocytes, but fewer bacterial revertants in the absence of S9 than the extract of 'nonsmoky' airborne particles. (17 Refs)

76. INDUCTION OF CYTOTOXICITY, MUTATION, CYTOGENETIC CHANGES, AND NEOPLASTIC TRANSFORMATION BY BENZO(A)PYRENE AND DERIVATIVES IN C3H/10T1/2 CLONE 8 MOUSE FIBROBLASTS.

Gehly EB, Landolph JR, Heidelberger C, Nagasawa H, Little JB
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Cancer Res; 42(5):1866-1875 1982

Benzo(a)pyrene (BaP), a series of its metabolic derivatives, and benzo(e)pyrene, a very weakly carcinogenic isomer, were tested for their biological effects on transformable C3H/10T1/2 cells. These cells were used as targets in a series of assays designed to measure oncogenic transformation, mutation to ouabain resistance, cytotoxicity, and induction of cytogenetic changes, as evidenced by chromosomal aberrations and sister chromatid exchange. Of all the compounds tested, only the parent hydrocarbon, BaP, and (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene were found to be significantly active in producing transformation and cytogenetic alterations. BaP, (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene, and (+-)-7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene however, were all effective inducers of mutation in C3H/10T1/2 cells. (+-)-7alpha,8beta-Dihydroxy-9beta,10beta-epoxy-7,8,9, 10-tetrahydrobenzo(a)pyrene was the most potent agent in tests for cytotoxicity Benzo(e)pyrene was inactive in all assays examined. Among the compounds tested, there was a correlation between the ability to induce cytogenetic changes and the ability to produce mutation and transformation. These results support the demonstrated role of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene as a proximal carcinogenic form of BaP and illustrate the utility of the C3H/10T1/2 cell system as an important tool for the detection of genotoxic damage by carcinogenic chemicals. (Author abstract) (47 Refs)

77. GENOTOXIC ACTIVITY OF FIVE ANTIDEPRESSANT HYDRAZINES IN A BATTERY OF IN VIVO AND IN VITRO SHORT TERM TESTS.

Brambilla G, Cavanna M, Faggin P, Pino A, Robbiano L, Bennicelli C, Zanacchi P, Camoirano A, De Flora S
Inst. Pharmacology, Univ. Genoa, Viale Benedetto XV, 2, I-16132 Genoa, Italy
J Toxicol Environ Health; 9(2):287-303 1982

The mutagenic and potential carcinogenic activity of iproniazid (IPZ), phenelzine (PHZ), nialamide (NLM), isocarboxazid (ICB), and mebanazine (MBZ) was assessed. Mouse liver and lung DNA damage was analyzed by the alkaline elution technique after single or daily, ip or po doses of each drug, ranging from 0.333 to 2x the LD50. ICB, NLM, PHZ, and MBZ caused significant DNA fragmentation with decreasing efficiency, while IPZ was ineffective. In contrast to ICB, NLM, and PHZ, MBZ induced DNA damage only in the lung and only after five successive daily doses. Sister chromatid exchange (SCE) in mouse bone marrow cells was assessed after ip administration of 1-2x the LD50 of each drug except MBZ. SCE frequencies in the IPZ, NLM, ISB, and PHZ treated groups increased 71%, 49%, 46%, and 34%, respectively, when compared with control groups. A dose-dependent increase in SCE frequency was observed in mice treated with ICB at LD50 and 2x LD50. Mutagenic activity was investigated with the Salmonella/microsome test. NLM and PHZ were mutagenic in the spot test (1 mg/plate) and the plate incorporation test (PIT). ICB and IPZ were not mutagenic, and MBZ was weakly mutagenic in the PIT. Antibacterial activity in repair deficient Escherichia coli was also assessed for each compound. ICB and IPZ were scarcely toxic, while NLM, PHZ, and MBZ showed significantly increased antibacterial activity in some E coli strains with spot and spiral tests. Long term carcinogenic tests should be performed for NLM and ICB, which are still in clinical use. (30 Refs)

78. MUTAGENICITY STUDIES WITH 2,4,5-T ON BACTERIA AND MAMMALIAN GERM CELLS.

Herbold BA, Machemer L, Rohrborn G
Inst. Toxicology, Bayer AG, Friedrich Ebert Strasse 217-219, D-5600 Wuppertal 1, W. Germany
Teratogenesis Carcinog Mutagen; 2(1):91-101 1982

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was tested for mutagenicity in an Ames mutagenicity with microsomal activation, a dominant lethal test in rats, and a cytogenetic assay of Chinese hamster spermatogonia. The 2,4,5-T contained 0.05 ppm dioxin. Salmonella strains used were TA 98, 100, 1535, and 1537, with cyclophosphamide and trypaflavine as controls. 2,4,5-T was tested at 4-2,500 ug/plate. In the dominant lethal test rats were fed 0.1, 1, or 100 mg/kg 2,4,5-T for 8 wk and then mated. Corpora lutea, dead, and viable embryos were counted 12 days after mating, and the rate of dominant lethal mutations determined. For the cytogenetic assay male Chinese hamsters were fed 0, 0.5, 5, or 50 mg/kg 2,4,5-T per day for 5 days in one test, and 0 and 500 mg/kg on the same schedule in a second test. The 2,4,5-T was not mutagenic in any of these tests. These findings are compared with tests of 2,4,5-T in other systems. (46 Refs)

79. EVALUATION OF THE CARCINOGENIC POTENTIAL OF 2,4-DINITROFLUOROBENZENE AND ITS IMPLICATIONS REGARDING MUTAGENICITY TESTING.

Warren ST, Dolittle DJ, Chang CC, Goodman JI, Trosko JE
Center for Genetics, Univ. Illinois at the Medical Center, Sch. Basic Medical Sciences, 808 S. Wood St., Chicago, IL, 60612
Carcinogenesis; 3(2):139-145 1982

Tumor promoters are compounds which dramatically enhance the appearance of tumors when chronically applied after an initiating dose of a carcinogen. Initiators are generally considered mutagens while promoters have previously been shown not to induce either DNA damage or mutations. 2,4-Dinitrofluorobenzene (2,4-DNFB), a compound used in the identification of N-terminal amino acids of polypeptides, has been previously reported to be a tumor promoter in mouse skin, while other investigators have found it to be a mutagen in bacteria and yeast. To investigate this apparent discrepancy, we chose to study the carcinogenic potential of 2,4-DNFB utilizing various methods available in V79 Chinese hamster cells. 2,4-DNFB exposure did not result in any unscheduled DNA synthesis, a measure of DNA excision repair, nor did it increase the frequency of sister chromatid exchanges in V79 cells either in the presence or absence of rat liver postmitochondrial supernatant (S-15). Forward mutations in V79 cells, either to ouabain or 6-thioguanine resistance, were not induced by 2,4-DNFB, in the presence or absence of S-15, 2,4-DNFB was, however, able to induce reversions in methionine-requiring E coli auxotrophs in a dose-dependent fashion. Phylogenetic differences between lower organisms and mammals may account for this discordance. 2,4-DNFB was found to inhibit metabolic cooperation, in a dose dependent manner, in V79 cells. This property has previously been shown to be correlated with tumor promoting ability in mouse skin. Therefore, we conclude that the carcinogenic potential of 2,4-DNFB might reside in its ability as a tumor promoter and not as a carcinogenic initiator. Furthermore, these studies serve to illustrate the need for caution when extrapolating bacterial data for risk assessment in humans. (Author abstract) (42 Refs)

80. MUTAGENICITY TESTING OF IRRADIATED ONIONS IN MICE.

Goud SN, Reddi OS, Reddy PP
Dept. Genetics, Osmania Univ., Hyderabad 500 007, India
Int J Radiat Biol; 41(3):347-349 1982

The mutagenic activity of irradiated onions was examined in Swiss albino male mice using the micronucleus test and the sperm head abnormality assay. No increase in the frequency of micronuclei occurred in mice fed either irradiated or unirradiated onions. Onions exposed to gamma rays did not significantly enhance the percentage of abnormal sperm. Freshly irradiated onions apparently do not possess any mutagenic activity evident from the above tests. (10 Refs)

81. PRELIMINARY EXPERIMENTAL CONTRIBUTION TO THE STUDY OF POSSIBLE CARCINOGENIC ACTIVITY OF TWO HERBICIDES CONTAINING ATRAZINE-SIMAZINE AND TRIFURALIN AS ACTIVE PRINCIPLES.

Donna A, Betta PG, Gagliardi F, Ghiazza GF, Gallareto M, Gabutto V
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Pathologica; 73(1027):707-721 1981

The carcinogenicity and mutagenicity of the herbicides Fogard S and Treflan were studied in vivo in female Swiss albino mice and in vitro in human lymphocyte cultures. The active principles in Fogard S are atrazine (25%) and simazine (37.5%). The active principle in Treflan is trifluralin (44.5%). Groups of 25 mice each received 0.25 ml of 2 ppm Fogard S or Treflan ip or sc, 13x at 3-day intervals. One animal from each group was killed every 15 days up to 7 mo. Necropsies were performed when possible on all animals. One mouse from the sc-Fogard S group, five from the ip Fogard S group, and four from the ip Treflan group were lost to cannibalism and could not be examined. Malignant lymphomas (ML) were found in three mice and mesothelioma (MT) in one mouse from the sc Fogard S group. ML was found in two mice from the ip Fogard S group. ML was found in five mice and MT in one from the sc Treflan group. ML was found in three mice and MT in three mice from the ip Treflan group. Cultures of human lymphocytes were stimulated with phytohemagglutinin and then exposed to 0.2, 0.1, or 0.05 cc of 2 ppm Treflan or 0.2, 0.05, or 0.01 cc of 2 ppm Fogard S. Fogard S did not produce abnormalities in morphology or chromosomal variations. At the higher dose, Fogard S produced a slight decrease in mitoses. Treflan produced significant decreases in the number of mitoses with increasing dose. Chromosomal abnormalities were produced in increased frequencies at the lowest dose. Results indicate a correlation between in vivo administration of either herbicide and tumor formation, as well as a correlation between in vitro Treflan administration and genetic abnormalities. (23 Refs)

REVIEWS AND OTHER RELATED STUDIES

82. TOXICOLOGY OF N-NITROSO COMPOUNDS.

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Ecotoxicol Environ Saf; 6(1):89-96 1982

Toxicology of N-nitroso compounds is discussed with respect to formation, carcinogenic effect of precursor amino compounds and nitrite, and significance to man. The potential nitrosation of drugs which are amine or amide derivatives or drug metabolic conversion products containing an amino group is of interest. Experimental evidence that N-nitroso compounds can be formed in vivo is reviewed; however, only a few studies have involved nitrosation conditions simulating those in the environment or in actual animal or human conditions. Standardized in vitro nitrosation assays that more accurately define conditions under which biological nitrosation occurs in the mammalian stomach would enhance our knowledge of in vivo nitrosation. The relationship between N-nitrosation, mutagenicity, and carcinogenicity based on previously reported data of relative in vitro nitrosatability of certain drugs, the mutagenicity of nitrosation products, and the carcinogenicity of the parent compounds when fed to rats concurrently with nitrite is tabulated. Very large differences between nitrosatability of different drugs are evident, establishing the nitrosation assay as a potentially useful screening procedure. A parallel relationship between nitrosatability of various drugs and mutagenicity is demonstrated. Presently, no evidence exists concerning the carcinogenic effect of N-nitroso compounds derived from drugs that are known to undergo nitrosation or to which man has been occupationally exposed. In vitro nitrosation studies have defined potential nitrosatable precursors and the conditions necessary for nitrosation. In vivo tests, with low levels of precursor amino compounds and/or nitrite, reveal levels of N-nitroso derivatives that are not in excess of low background levels. (31 Refs)

83. CAN WE DETERMINE MUTAGENICITY OR ONLY A MUTAGENIC POTENTIAL?

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Mutat Res; 92(1/2):3-7 1982

When an agent is identified as a 'mutagen', the assay results have identified only the agent's mutagenic potential, whose expression in a given biosphere can be masked by detoxification mechanisms and/or altered by metabolic activation. Certain types of mutagens may at present be overlooked because most assays of environmental mutagenicity ignore chromosomal malsegregation. The assessment of the mutagenic potential of a given agent in man requires the evaluation of all potential sources of its metabolic activation. It is almost impossible to detect and test all potentially mutagenic metabolites of a given agent. (15 Refs)

84. EXAMPLES OF TESTING AGAINST ORDERED ALTERNATIVES IN THE ANALYSIS OF MUTAGENICITY DATA.

Boyd MN
Dept. Biostatistics, Sch. Public Health, Univ. North Carolina Chapel Hill, Rosenau Hall 201 H, Chapel Hill, NC, 27514
Mutat Res; 97(2):147-153 1982

Three statistical procedures testing against ordered alternatives were used to analyze a set of mutagenicity data. Two tests (Jonckheere and Chacko) are non-parametric; the third (aligned rank order test) involves correlating aligned mean concentrations with predicted concentration rankings. Standard analysis of variance may not be appropriate if the experimental conditions do not satisfy the usual assumptions. Non-parametric tests are particularly appropriate when sample sizes are small. The powers and efficiencies of the tests were not compared. All of the tests are sensitive to increasing mutation frequency as a function of increased concentration of the suspected mutagen. (10 Refs)

85. IS COFFEE DRINKING A HEALTH HAZARD?

Chaudhuri MM, Ghosh S
Botany Dept., Bose Inst., Calcutta 700009, India
Sci Culture; 47(5):157-160 1981

Whether caffeine or its derivatives is a health hazard is discussed with respect to chemistry, metabolism, and mutagenicity testing. Evidence suggests that caffeine at low doses may act as a stimulator of the nervous system. High consumption, particularly in pathological conditions, may be hazardous. The dose of caffeine required for embryotoxicity is 100 mg/kg (equivalent to 40 cups of coffee). Mutagenicity testing has led to various conflicting results: caffeine has been found to be nonmutagenic, comutagenic, or a potent mutagen, particularly at high doses. (44 Refs)

86. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.

Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

Governmental agencies charged with protecting the public from harmful chemicals have developed policies for identification, characterization, and control of potential human carcinogens. Scientific issues are discussed with respect to evidence for identification of a carcinogen (epidemiological, rodent carcinogenicity bioassays, short-term tests, chemical structure), predictability of animal tests for humans, the rodent bioassay (study design, statistical analysis, tumor classification), qualitative and quantitative risk assessment, and mechanisms of carcinogenesis (epigenetic and genetic, ultimate carcinogen vs procarcinogen). Historical emergence of a carcinogen policy is reviewed with respect to legislative strategies, scientific vs regulatory decision making, and the Environmental Protection Agency's principles and Occupational Safety and Health Act's generic carcinogen policy. The impact of carcinogenicity on medicinal research programs involves earlier screening for potential carcinogenicity, product contaminants and breakdown products, workplace safety and toxic waste disposal, commitment to bioassays before therapeutic value to man is known, and the Food and Drug Administration Bureau of Drugs guidelines and Bureau of Foods structure guide. The attempt to separate the scientific risk assessment from the regulatory political/societal decision-making is a significant feature of the evolving carcinogen policy of the regulators. This approach should eliminate the hidden human bias from the scientific assessment and allow for updating the scientific decision based on newer scientific knowledge. (37 Refs)

87. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.

Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

Genetic hazards associated with the production and use of synthetic and natural dyes used as food additives are reviewed. Genotoxicity of structurally-related azo, triphenylmethane and xanthene dyestuffs used in drugs and cosmetics was considered. Particular attention was given aminoazobenzene and several of its derivatives with respect to carcinogenicity and mutagenicity. Activities of these dyes in short-term tests for genotoxicity are stressed; animal carcinogenicity and nonspecific toxicity is not emphasized. Dye metabolism and activities of dye metabolites are reviewed. Structural features of these dyes and their metabolites were assessed and an attempt was made to evaluate data with respect to correlations with tumor-inducing ability and to levels of environmental exposure. More than half of the dyes discussed have shown activity in at least one short-term test. Certain food colors may be active in vitro at levels comparable to those ingested daily. Natural colors, except for curcumin and riboflavin, were inactive. More data are required for all of the various dye groups, particularly for synthetic and natural non-azo compounds. Discussion of structure-activity must be tentative because of the lack of data and problems due to active sample contaminants. The presence of various substituents may be potentiating. No currently permitted food color which is inactive in short-term tests is considered a carcinogen, although some active colors require further animal testing. A human cancer hazard may exist where significant amounts of finished benzidine dye samples are handled. Such risks from exposures to other colors and the possibility of human germ-line mutation induction by dyes cannot be assessed in a meaningful manner. (365 Refs)

88. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.

Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

The purpose of this document is to review critically the information on the mutagenicity and other genotoxic effects of the developing direct coal liquefaction technology. The goal is to evaluate the potential health effects on humans and to make recommendations for action that might be taken to minimize them. The main conclusions are that the materials produced by direct coal liquefaction often contain a higher level of genotoxic compounds than comparable materials from other liquid fossil fuel technologies, that combined chemical and biological assay has made possible considerable progress in identifying the chemical substances responsible for this difference, and that there are ways to modify the technology that might eliminate many if not all of these genotoxic compounds. The review consists of six chapters. The first three are essentially introductions to genotoxicity testing and to the theories back of it, to the technology of direct coal liquefaction, and to the chemistry involved in analyzing and preparing for biological testing of the materials from the technology. The fourth chapter concerns tests for genotoxicity of the compounds and compound classes that have been identified by chemical analysis as present in such materials. The fifth chapter concerns tests for genotoxicity of the materials from the technology. The final chapter summarizes the conclusions that can be drawn from these tests and makes recommendations concerning future research and other activities to define better and to minimize the potential genotoxic effects of the technology. (Author abstract)

89. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.

Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

Carcinogenicity of environmental benzo(a)pyrene (BAP) is reviewed. BAP is a polycyclic aromatic hydrocarbon consisting of five aromatic rings that is formed during combustion of fossil fuels; the compound is the most important carcinogen in soot, cigarette smoke, coal gasification effluent, and coke oven emissions. Three sources are expected to increase atmospheric levels due to energy/fuel conservation: stationary combustion of coal and synthetic fuels and increased use of diesel fuel by automobiles. The primary route of human exposure to BAP is inhalation, where the compound is deposited in the lower lung and eluted into surrounding tissue. Most carcinogens are thought to act through strong electrophilic metabolites which bind covalently to DNA of the lung. Animal data indicate that the action of BAP is enhanced by other chemicals such as sulfur dioxide and other irritant gases. A threshold dose for BAP has not been found; the effect of small doses of BAP may be greater than that for a single high dose. Mixtures containing BAP (urban air, industrial emission, cigarette smoke) result in increased carcinogenic effect. Since the early 1970's BAP has tested positive in 20 in vitro short term test systems considered predictive for human carcinogenicity/mutagenicity. Quantitative risk assessment for BAP is confounded by problems in extrapolating high doses in small animal studies to low doses in humans and by the variables involved in monitoring data. (186 Refs)

90. REPORT OF THE FEDERAL PANEL ON FORMALDEHYDE.

Griesemer RA, Ulsamer AG, Arcos JC, Beall JR, Blair AE, Collins TF, De Serres FJ, Everson RB, Gamble JF, Gaylor DW, Groth DH, Kang HK, Keenlyside RA, Lloyd JW, Nettesheim P, Saffiotti U, Weisburger EK

Oak Ridge Natl. Lab., Oak Ridge, TN

Environ Health Perspect; 43:139-168 1982

The Federal Panel on Formaldehyde concluded that definitive experiments exist which demonstrate the mutagenicity and carcinogenicity of formaldehyde under laboratory conditions. Formaldehyde induces both gene mutations and chromosomal aberrations in a variety of test systems. Inhalation of formaldehyde causes cancer of the nose in rats. The concentrations of formaldehyde in inhaled air that caused nasal cancer in Fisher 344 rats are within the same order of magnitude as those to which humans may be exposed. The data presently available do not permit a direct assessment of the carcinogenicity of formaldehyde to man. Epidemiologic studies on exposed human populations are in progress and may further clarify the situation. Other experimental and human studies on toxic effects such as teratogenicity and reproductive disorders are as yet inadequate for a health risk assessment. The CIIT 24 mo study on animal carcinogenicity has not yet been completely evaluated. Additional data are expected on the effect of prolonged exposure to lower doses of formaldehyde and on the possible carcinogenicity of formaldehyde in the mouse. The panel recommends that, for a comprehensive health risk assessment, further experiments be conducted on the effects of other modes of exposure (ingestion and skin penetration), the effects in humans, and on the pharmacokinetics of formaldehyde in man and animals and the possible role for formaldehyde in reproductive and chronic respiratory disorders. It is the conclusion of the panel that formaldehyde should be presumed to pose a carcinogenic risk to humans. (Author abstract) (143 Refs)

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2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
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Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
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3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
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Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
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10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

SERIES CK19 No. 82/09

SEPTEMBER, 1982

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IN VIVO TESTS FOR MUTAGENICITY

1. STUDIES IN THE INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA MELANOGASTER BY NITROHETEROCYCLIC COMPOUNDS.

Kramers PG
Natl. Inst. Public Health, P.O. Box 1, Bilthoven, The Netherlands
Mutat Res; 101(3):209-236 1982

The induction of sex-linked recessive lethals in Drosophila melanogaster by 24 nitroheterocyclic compounds was investigated. The adult feeding technique was used in most cases, and injection and larval feeding in others. Of the nitroimida-

HE 20.3173/2:

zoles tested, toxicity increased in the order metronidazole, nimorazole, ronidazole, dimetridazole. Among the nitrofurans, only nitrovin, furazolidone, and furaltadone were clearly mutagenic. Nitrofurantoin and niridazole were ambiguous. Nitrofurans were active at lower molar concentrations than were nitroimidazoles. 4-Nitroquinoline oxide was clearly mutagenic when fed to larvae. Drosophila gut flora were shown not to play role in the activation of ZK 26.173 and furazolidine to mutagenic metabolites. Activation of ZK 26.173 was significantly inhibited in Drosophila strains lacking xanthine dehydrogenase and aldehyde oxidase. (72 Refs)

2. LACK OF ASSOCIATION BETWEEN INDUCTION OF DOMINANT-LETHAL MUTATIONS AND INDUCTION OF HERITABLE TRANSLOCATIONS WITH BENZO(A)PYRENE IN POSTMEIOTIC GERM CELLS OF MALE MICE.

Generoso WM, Cain KT, Hellwig CS, Cacheiro NL
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 94(1):155-163 1982

Benzo(a)pyrene (BP) was tested for its ability to induce dominant-lethal mutations in germ cells of (101 x C3H)F1 male mice. A dose of 500 mg/ml BP, which inhibits the ability of male mice to mate, was administered ip in a single injection. Serial matings indicated dominant-lethal effects in the intervals 4.5-5.5 and 6.5-7.5 days, corresponding to early and middle spermatozoa, and possibly in the intervals 32.5-33.5 and 34.5-35.5 days, corresponding to preleptotene spermatocytes. Dominant lethal effects were clear-cut in matings in the interval 3.5-7.5 days after treatment. The yield of BP-induced dominant-lethal effects in these stages was also affected by the stock of untreated females used, possibly due to the differential ability of fertilized eggs to repair BP-induced lesions in the fertilizing sperm. Of the total 548 male progeny analyzed from two stocks of mothers, only one was found to be a carrier of a reciprocal translocation. These results indicate that BP is effective in inducing dominant lethal mutations but relatively ineffective in inducing heritable translocations in male postmeiotic germ cells. (9 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

3. LACK OF MUTAGENICITY BY NATURAL AND SYNTHETIC SEX HORMONES IN EPITHELIAL HUMAN CELLS (MEETING ABSTRACT)

Ferreri AM, Capucci A, Rocchi P, Prodi G
Institute di Cancerologia, Universita di Bologna, Bologna, Italy
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The mutagenic power of 17beta-estradiol and its synthetic analogous diethylstilbestrol was tested in a human cell line (EUE). Five concentrations of both hormones were used (from 10-5M up to 10-10M) and cells were exposed to these compounds for 24 hrs. To assay the mutagenic action we used selection against diphtheria toxin, a protein synthesis inhibitor, in a dose of 0.05 Lf/ml; spontaneous stable mutants resistant to this drug are present in EUE cells at a frequency of 0-8x10(-6). The mutagenic power of each tested dose was assayed after expression times of 7 and 21 days: in all the experiments performed no mutagenicity by 17beta-estradiol and diethylstilbestrol was seen at any of the concentrations tested. These results may indicate that the compounds are not mutagenic, or that they are mutagenic but not detected as such by these experimental conditions. (1 Ref)

MICROBIAL TESTS FOR MUTAGENICITY

4. THE STUDY ON THE MUTAGENIC ACTIVITY OF URINE FROM THE PATIENTS RECEIVING ANTI-CANCER DRUGS.

Pak K, Miyakawa M, Yoshida O
Dept. Urology, Shiga Univ. Medical Science, Japan
Hinyokika Kiyo; 27(12):1481-1495 1981

Mutagenic activity of urine from 43 patients with urogenital cancer was tested in the Salmonella typhimurium TA98 and TA100. Ninety-four urine samples were divided into four groups: Group 1, from patients receiving no drugs; Group 2 from patients receiving some drugs except for anti-cancer drugs; Group 3, from patients receiving single anti-cancer drug; Group 4, from patients receiving two anti-cancer drugs. A 24-hr urine was collected for Groups 1 and 2, and a urine from the time of administration to the next early morning was collected for Groups 3 and 4. No concentrates of Group 1 were mutagenic to either strain TA98 or TA100. No concentrates of Group 2 were mutagenic to either strain TA98 or TA100. Eight urine concentrates of Group 3 were mutagenic. The urine concentrate obtained after administration of cyclophosphamide was mutagenic to the strain TA100. Four concentrates from patients receiving adriamycin were mutagenic to the strain TA98 and/or TA100 and two urine concentrates were mutagenic to both strain TA98 and TA100. Two concentrates from patients receiving cis-diamminedichloride platinum were mutagenic to the strain TA100. Four urine concentrates of Group 4 were mutagenic. Both concentrates from the patients receiving adriamycin and 5-fluorouracil were mutagenic to the strain TA98. One urine concentrate from the patients receiving mitomycin C and cytosine arabinoside was mutagenic to the strain TA98. The concentrate from the patient receiving vincristine and actinomycin D was mutagenic to the strain TA98. Our results suggest that urinary metabolites of some anti-cancer drugs might act as an initiator on the urothelium. Although at the present time the detection of mutagenic activity in the urine does not necessarily predict carcinogenesis of the urothelium, the physician who uses anti-cancer drugs should be aware of delayed sequelae on the urinary tract. (77 Refs) (In JPN)

5. FAECAL MUTAGENESIS AND COLONIC CANCER.

Askew AR, Ward M, Green MK, Reibelt LD
Dept. Surgery, Royal Brisbane Hosp., Herston 4029, Australia
Aust NZ J Surg; 52(1):27-29 1982

The incidence of fecal mutagens has been evaluated using the Ames Test in 16 patients with proven colon cancer and 35 volunteers with no symptoms referable to the colon and a negative hemoccult test. Twenty-five percent of the cancer patients, and 20% of the volunteers had mutagen positive feces. These results suggest that the incidence of fecal mutagens in patients with colon cancer is similar to that found in a population with a high risk of developing colonic neoplasms. (Author abstract) (8 Refs)

6. METABOLISM OF THE MUTAGENIC ENVIRONMENTAL POLLUTANT, 6-NITROBENZO[A]PYRENE: METABOLIC ACTIVATION VIA RING OXIDATION.

Fu PP, Chou MW, Yang SK, Beland FA, Kadlubar FF, Casciano DA, Heflich RH, Evans FE
Natl. Center for Toxicological Res., Jefferson, AR, 72079
Biochem Biophys Res Commun; 105(3):1037-1943 1982

The effect of 6-nitro substitution on the metabolic activation of the parent compound, benzo(a)pyrene, and on mutagenic activation in the Salmonella typhimurium/microsome reversion assay was investigated. Separation of 6-nitro-BP metabolites was effected using reversed-phase high pressure liquid chromatography. The monohydroxylated 6-nitro-BP metabolites were the most active mutagens in the Ames assay, suggesting that these compounds were the proximal mutagens. (16 Refs)

7. MUTAGENICITY OF DIBROMODULCITOL (DBD, AN ALKYLATING ANTICANCER DRUG) AND ITS MONO- AND BIFUNCTIONAL CONVERSION PRODUCTS STUDIED BY THE SALMONELLA/MICROSOME ASSAY.

Toth K, Sugar J, Somfai-Relle S, Hedegus L
Natl. Oncological Inst., Res. Inst. Oncopathology, Rath Gyorgy-u. 7-9, H-1122 Budapest, Hungary
Carcinogenesis; 3(3):333-336 1982

Dibromodulcitol (DBD) and one of its most important bifunctional transformation products, dianhydrogalactitol (DAG) with similar cytostatic effect, were tested by the Salmonella/microsome assay on strains TA 1535, TA 1538, TA 98 and TA 100 using the plate incorporation technique. Both drugs were direct mutagens in strains TA 1535 and TA 100 and non-mutagenic in other strains. Their mutagenic effect was not influenced by S-9 mix from rat liver. Mutagenicity of DAG was very limited because of its marked toxicity. The other monofunctional alkylating derivatives, ie, 1-bromo-3,6-anhydrodulcitol and 1,2-epoxy-3,6-anhydrodulcitol were highly mutagenic in strains TA 1535 and TA 100 with and without S-9 mix despite having no anticancer effect. Anticancer activity was exerted only by the bifunctional alkylating hexitols (DBD, DAG) which showed moderate mutagenic activity compared to the monofunctional derivatives. No correlation could be established between the mutagenic and anticancer effect of the four structurally related hexitols. Mutagenicity of urine and bile from rats after a single administration of the max tolerated (450 mg/kg) dose of DBD was also examined, and the hexitol components of the same urine sample were identified by the DBD and its mutagenic transformation products were excreted in urine and not through the bile. The mutagenic effect of DBD observed cannot be attributed exclusively to DBD itself, because the parent molecule, like other alkylating agents, easily undergoes spontaneous decomposition under in vitro and in vivo conditions to release both bi- and monofunctional alkylating solvolysis products and these highly reactive derivatives may play a role in this effect. No significant difference in the relative mutagenicity was detected between DBD and cyclophosphamide, used as a reference substance (Author abstract) (38 Refs)

8. MUTAGENICITY IN SALMONELLA TYPHIMURIUM AND STRUCTURE-ACTIVITY RELATIONSHIPS OF WASTEWATER COMPONENTS EMANATING FROM THE MANUFACTURE OF TRINITROTOLUENE.

Spanggord RJ, Mortelmans KE, Griffin AF, Simmon VF
SRI International, Menlo Park, CA, 94025
Environ Mutagen; 4(2):163-179 1982

Mutagenic screening of 36 polynitroaromatic compounds in wastewater of a plant that manufactures 2,4,6-trinitrotoluene (TNT) was accomplished with strains TA1535, TA1537, TA1538, TA98, and TA100 of Salmonella typhimurium using the Ames test with and without microsome S-9 mix from Sprague-Dawley rats. Five dose levels ranging up to 5,000 ug/plate were used. Combinations of the wastewater components to yield a synthetic condensate blend were mutagenic in all 5 strains with and without metabolic metabolic activation. The most active compounds as determined by mutagenic potency with strain TA100 were 2,4,5-TNT greater than 3,5-dinitroaniline greater than 1,3,5-trinitrobenzene, which occur as trace elements in the discharge from munitions production facilities. The three components represent 0.6% of the waste, but account for approx 20% of the mutagenic potency of the wastewater. Over 80% of the compounds tested were mutagenic in either strain TA98 or TA100. Generally compounds showing activity with or without S-9 were more mutagenic in the absence of metabolic activation. Mutagenicity of polynitroaromatic compounds in S typhimurium depends primarily on the nitroreductase activity of the strains; enzymatic reduction is favored by para orientation of nitro groups in TNTs, aminodinitrotoluenes, and dinitrotoluenes. (20 Refs)

9. BIOLOGICALLY ACTIVE AROMATIC AMINES DERIVED FROM CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS: SYNTHESIS AND MUTAGENICITY OF AMINOBENZO(A)PYRENES.

Fu PP, Heflich RH, Casciano DA, Huang AY, Trie WM, Kadlubar FF, Beland FA
Natl. Center for Toxicological Res., Food and Drug Admin., Dept. Health and Human Services, Jefferson, AR, 72079
Mutat Res; 94(1):13-21 1982

The mutagenicities of 6-amino-benzo(a)pyrene (6-NH2-BP), three K-region NH2-BPs (4-amino-benzo(a)pyrene, 11-amino-benzo(a)pyrene and 12-amino-benzo(a)pyrene), and two N,N-diacetyl derivatives, (4-N(acetyl)-2-benzo(a)pyrene and 12-N(acetyl)2-benzo(a)pyrene) were examined in the Ames' tester strains TA1535, TA1538, TA98 and TA100 and compared to those of the parent compound, benzo(a)pyrene (BP), and of 2-aminofluorene (AF). In the absence of S9 activation only 6-NH2-BP and high doses of AF induced revertants and only in the tester strains sensitive to frameshift mutagens. In the presence of S9, all the compounds were active in TA100, TA98, and TA1538, but none were mutagenic in TA1535. A dose response was observed for each compound. The N,N-diacetyl derivatives were less mutagenic than their parent amines. At high concentrations, however, there was a decrease in mutagenicity for 4-and 12-NH2-BP which was not found with the diacetyl derivatives. The 4-substituted analogues were clearly the most mutagenic in TA98, with a general order of mutagenicity of 4-NH2-BP greater than 4-N(Ac)2-BP greater than 12-NH2-BP greater than 12-N(Ac)2-BP greater than AF greater than 11-NH2-BP approx = BP greater than 6-NH2-BP. The 4-NH2-BP derivatives were also the most active in TA100. While paraoxon had no effect on the overall activity of 4-NH2-BP in either strain, it did decrease the mutagenicity of 4-N(Ac)2-BP by 75%. These data suggest that arylamines derived from carcinogenic polycyclic aromatic hydrocarbons are activated to potent mutagens primarily through S9-mediated metabolism of the parent amine. (13 Refs)

10. PH-SENSITIVE MUTAGENIC ACTIVITY OF OZONE-TREATED 1,2-DIMETHYLHYDRAZINE IN THE SALMONELLA/MICROSOME ASSAY.

Chambers TM, Burleson GR
(c/o Burleson) Lobund Lab., Dept. Microbiology, Univ. Nortre Dame, Notre Dame, IN, 46556
Mutat Res; 94(1):23-29 1982

It has been previously shown that ozonation of 1,2-dimethylhydrazine (DMH) converts this normally inactive compound into a chemical species capable of inducing revertants in the Ames Salmonella typhimurium/microsome assay. It is shown that the mutagenicity of this ozonation-induced product is pH-dependent. The product of ozonation in basic solution was not mutagenic, while the product of ozonation in acidic solution was highly mutagenic. The mutagenic product was inactivated by raising the pH. Mutagenicity of ozonated DMH was detected at concentrations as low as 30 ug/ml at pH 2.5, and 60 ug/ml at pH 7. Toxicity to TA1535 was observed at pH 2.5 at concentrations greater than 600 ug/ml, while DMH ozonated at pH 7 was not toxic at concentrations as great as 3 mg/ml. Spontaneous reversion frequency was not affected by sample pH. These results suggest that ozonation produces a mutagen that is stable in acid but is labile at high pH. That hydrazines may be an exception to the phenomenon of inactivation of chemical carcinogens by ozonation is discussed in light of the use of ozonation in waste water treatment. (20 Refs)

11. PHOTODYNAMIC EFFECTS OF DYES ON BACTERIA. V. MUTAGENESIS BY ACRIDINE ORANGE AND 46-NM OR 500-NM LIGHT IN STRAINS OF ESCHERICHIA COLI THAT DIFFER IN REPAIR CAPABILITY.

Hass BS, Webb RB
Shell Development Co., Westhollow Res. Center, Box 822, Houston, TX, 77001
Mutat Res; 94(1):39-51 1982

The effect of acridine orange (AO) and 460 nanometer (nm)- or 500-nm light on mutagenesis in strains of Escherichia coli differing in repair capabilities was investigated. It had been previously shown that AO is a weak to moderate dark mutagen in all strains tested except for the wild-type strain WP2. When irradiated with 460 nm light, in the presence of AO WP2s showed a mutation rate significantly lower than wild-type. Results comparing the effects of 460 nm light to 500 nm light suggest that the uvrA+(endonuclease) gene product does not effectively contribute to the repair of the lesions produced by AO and 460 nm light. DNA lesions responsible for mutation induction in strains WP10, WP6, and Bs-1 by AO and 460 nm light are different from those produced by AO and 500 nm light. Endonuclease repair can affect the mutagenic response to AO in the dark. DNA lesions induced by AO and 500 nm light are not effectively repaired by the uvrA endonuclease, and the effect of the absence of the uvrA endonuclease was even greater with externally bound AO. With 460 nm light, the mutation rate in the uvrA strain WP2s was 0.31 of the value of the wild-type strain WP2. Thus the absence of the uvrA endonuclease increased the dark AO mutation rate, but decreased the photodynamic mutation rate obtained with AO plus light at either wavelength. It appears that uvrA strains may be inadequate for identifying some classes of mutagens. The relatively high rates of mutation in the wild-type and po1A strains tested suggest that such strains should be included in mutagen screening programs. (26 Refs)

12. MUTAGENICITY OF 4,4'-METHYLENEDIANILINE DERIVATIVES IN THE SALMONELLA HISTIDINE REVERSION ASSAY.

Rao TK, Dorsey GF, Allen BE, Epler JL
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Arch Toxicol; 49(3/4):185-190 1982

The compound 4,4'-methylenedianiline and its derivatives were assayed for mutagenicity in the Salmonella/microsomal mutagenicity assay developed by Ames. A specificity to revert strain TA98 suggests a mechanism of frameshift mutagenesis. Liver microsomal preparations (S-9) from rats induced with phenobarbital were most effective for metabolic activation. Alkyl substitution of 4,4'-methylenedianiline did not alter its mutagenic activity; however, substitution of both positions ortho to the amino group eliminated mutagenic activity. Substitution with alkoxy-carbonyl groups eliminated mutagenic activity, whereas halogen substitution (chlorine, fluorine) enhanced the mutagenicity activity. The results presented here show the use of structure-activity studies as predictive tools for the assessment of genotoxic properties of industrial chemicals. (Author abstract) (14 Refs)

13. MUTAGENICITY OF SOME INDOLES AND RELATED COMPOUNDS IN THE AMES TEST.

Curvall M, Florin I, Jansson T
Res. Dept., Swedish Tobacco Co., P.O. Box 17007, S-104 62 Stockholm, Sweden
Toxicology; 23(1):1-10 1982

Nineteen indole derivatives and three analogues were studied with the Ames test using strain TA98. All compounds were tested at 12 different dose levels (3 nanomol to 30 umol/plate). Indole and all monosubstituted indoles were inactive, whereas 2,3-dimethylindole, 2,3,5-trimethylindole, and 2,3,6-trimethylindole were mutagenic; activity of the two mutagenic trimethylindoles was of the same order of magnitude and markedly exceeded that of the mutagenic dimethylindole. Mutagenicity was unaffected by S-9 from Aroclor-induced rats. When the 5-methyl group in 2,3,5-trimethylindole was exchanged for a methoxy group or a nitro group, and when the aromatic ring system of 2,3-dimethylindole was extended to that of 2,3-dimethylbenz(g)indole, mutagenic effects were lost. It was concluded that 2,3-dimethyl substitution of the indole ring is essential for mutagenic activity. (24 Refs)

14. MICROBIOLOGICALLY-MEDIATED MUTAGENIC ACTIVITY OF CRUDE OIL.

Cummings BA, Gordon RC
Dept. Microbiology, Colorado State Univ., Fort Collins, CO
Microbiologically-mediated Mutagenic Activity of Crude Oil. Available from National Technical Information Service, Springfield, VA, as PB82-105131:, 302 pp., 1981.

Crude oil was incubated with raw and sterile river water samples and assayed for mutagenic activity by the Ames test to determine the ability of naturally-occurring freshwater microorganisms to form mutagenic biodegradation products from crude oil. River water samples supplemented with inorganic salts were incubated with one percent crude oil in Erlenmeyer flasks for 1-6 wk and 4 and 20 C with shaking. Replicate flasks were extracted at various time intervals with 1,1,2-trichloro-1,2,2-trifluoroethane, the solvent evaporated and the residues taken up in dimethyl sulfoxide for mutagenicity testing. The extracts were assayed for mutagenic activity by the plate incorporation method of the Ames test with Salmonella tester strains TA 100, TA 1535, TA 1537, TA 1538 and TA 98.

Mammalian liver microsomes were not used in the mutagenicity test system as the oil-degrading microorganisms constituted the enzyme activation system in this study. Preliminary studies in Colorado with lagoon water and Black Hollow, Colorado crude oil showed that frameshift mutagens were produced during microbial degradation of the oil. Studies in Alaska with Chena River water and Prudhoe Bay, Alaska crude oil showed that both frameshift and base-pair substitution mutagens were present in the oil after microbial degradation. Mutagenic activity was not detected in either of the crude oils tested prior to incubation. The presence of mutagenic products may be related to the presence of mutagenic products in microbiologically-degraded crude oil. (Author abstract)

15. MUTAGENICITY OF PYROLYSATES FROM GUANIDINE, UREIDE, SECONDARY AMINES AND POLYAMINES FOUND BY THE SALMONELLA/ MAMMALIAN-MICROSOME TEST.

Ohe T
Kyoto City Inst./Public Health, 1-2, Higashi-Takadacho, Mibu, Nakagyoku, Kyoto 604, Japan
Mutat Res; 101(3):175-187 1982

The mutagenicity of pyrolysates formed from various nitrogenous compounds at 300, 400, 500 and 600 C were assayed in the Salmonella/mammalian-microsome test. Compounds subjected to pyrolysis included guanidine, ureide, and a variety of secondary and polyamines. Pyrolysates from methylguanidine, agmatine, dihydrouracil, dimethylamine, diethylamine, trimethylamine, triethylamine, pyrrolidine, morpholine, sarcosine, piperazine, piperidine, spermine and spermidine were found to be mutagenic. Mutagenicity began to be evident for pyrolysates obtained at temperatures 400-600 C (was highest for 600 C-except for that derived from methyl-guanidine) when S-9 mixture was added. Pyrolysates from morpholine, piperazine, piperidine, spermine and spermidine were toxic for TA98 and TA 100, while those from dimethylamine and diethylamine were toxic for TA98. The pyrolysate from proline had the highest mutagenic activity, on both TA 98 and TA 100, (with metabolic activation). With metabolic activation, the number of revertants of TA 98 induced by the pyrolysates was greater than those of TA 100. Pyrolysates from dimethylamine, diethylamine and pyrrolidine were slightly mutagenic toward TA 100 in the absence of microsomal activation. (44 Refs)

16. INDUCTION OF MITOTIC GENE CONVERSION BY BROWNING REACTION PRODUCTIONS AND ITS MODULATION BY NATURALLY OCCURRING AGENTS.

Rosin MP, Stich HF, Porie WD, Wu CH
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Center, 601 West 10th Ave., Vancouver, British Columbia V6T 1W5, Canada
Mutat Res; 101(3):189-197 1982

Models were developed to simulate caramelization and Mailard reactions, and the effects of heating to normal cooking temperatures single sugars or sugars and amino acid mixtures were tested. The modulating effect of the trace metals iron, copper and manganese, and selenite on the genotoxicity of the browning reaction products of a heated glucose-lysine solution and a commercial-grade caramel powder were investigated in these model systems. The conversion frequency of logarithmically growing yeast was enhanced up to 15 times after exposure to a heated glucose-lysine mixture. Equimolar concentrations of unheated glucose-lysine mixture did not possess convertogenic activity. Addition of S-9 fraction completely suppressed convertogenic activity of heated solution and prevented toxicity at higher concentrations. Results using caramel power paralleled those above, except that caramel requires no further heating. Metals added to growing cultures did not themselves alter conversion frequency from that observed in controls. In the presence of iron (III) convertogenic activity induced by heated glucose-lysine mixtures was completely suppressed. Copper (II) reduced yield of convertants, while manganese (II) and sodium selenite were without effect. Similar results were obtained with these metals in cultures treated with caramel. Protective mechanisms are discussed. (34 Refs)

17. MUTAGENICITY SCREENING OF TWENTY-FIVE COSMETIC INGREDIENTS WITH THE SALMONELLA/ MICROSOME TEST.

Blevins RD, Taylor DE
Div. Health Sciences, East Tennessee State Univ., Box 22690-A, Johnson City, TN, 37614
J Environ Sci Health [A]; 17(2):217-239 1982

Nine of 25 cosmetic ingredients tested demonstrated potential mutagenicity in the qualitative spot test in Salmonella histidine auxotrophs. Only one of the nine ingredients, DEA laureth sulfate, gave a dose-related 4.3-fold increase in colony counts in the plate incorporation test at the highest non-inhibitory dose with strain TA98 and no S9 mix. (33 Refs)

18. EFFECT OF 4'-HALOGEN SUBSTITUTION ON THE MUTAGENICITY OF TRANS-4-ACETAMIDOSTILBENE AND TRANS-4-(N-HYDROXYACETAMIDO)STILBENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

Shirota FN, Hanna PE
(c/o Hanna) Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Med Chem; 25(5):593-595 1982

The effect of halogen substituents placed at the 4' position of trans-4-acetamidostilbene (1, AAS) to alter the pattern of biotransformation and thus the mutagenicity of these derivatives was evaluated by comparing the mutagenic effects of 1 on Salmonella typhimurium TA-100 with the corresponding 4'-F (2), 4'-Cl (3), and 4'-Br (4) analogues. The mutagenic properties of trans-4-(N-hydroxyacetamido)stilbene (5) and its 4'-F (6), 4'-Cl (7), and 4'-Br (8) derivatives were also evaluated in this system. Both the amides (1-4) and hydroxamic acids (5-8) required the presence of a metabolic activating system prepared from hamster liver in order to produce a mutagenic effect. All of these compounds were mutagenic to TA-100. Their mutagenic potencies were markedly influenced by the 4'-halogen substituents, the relative mutagenic potencies of the amides being 2 (4'-F) greater than 1 (4'-H), 3 (4'-Cl) greater than 4 (4'-Br), while the hydroxamic acids followed the order of 1 (4'-H) greater than 2 (4'-F) greater than 3 (4'-Cl), 4 (4'-Br). (Author abstract) (17 Refs)

19. MUTAGENICITY, CARCINOGENICITY, AND BIOCHEMICAL ACTIVITY OF ELEVEN NEW 5-NITROFURAN ANALOGS (MEETING ABSTRACT)

Erturk E, Swaminathan S, Ichikawa M, Bryan GT
University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Fed Proc; 41(3):330 1982

New analogs of the bladder carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, (FANFT), were synthesized and tested for antibacterial activity against Esherichia Coli and Staphylococcus Aureus, and for mutagenicity against Salmonella TA100 (Ames test). Two compounds were further tested for their ability to induce ornithine decarboxylase (ODC) in the urinary bladder, and for their carcinogenicity in female rats after 46 wks of exposure in diet followed by 20 wks of control feed. The test compounds were: 2-formylamino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (I), 2-amino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (II), 5-nitro-3,4-diphenyl-2-methyl furoate (III), 5-hydroxylamino-3,4-diphenyl-2-methyl furoate (IV), 5-amino-3,4-diphenyl-2-methyl furoate (V), methyl(2-oxy-3,4-diphenyl-4-cyano)butanoate (VI), methyl(2-oxy-3,4-diphenyl-4-cyano)butenoate (VII), 2,5-dioxy-3,4-diphenyl-3-pyrroline (VIII), 5-(N-acetylamino)-3,4-diphenyl-2-methyl furoate (IX), 5-(N,N-diacetylamino)-3,4-diphenyl-2-methyl furoate (X), and 5-(N-acetylamino)-2-(2-thiazolyl) furane (XI). I and II, the vinyl bridged analogs of FANFT, showed antibacterial activity against both bacteria, were mutagenic to TA-100, and induced urinary bladder ODC; however, they were not carcinogenic in rats. III was antibacterial and mutagenic, and other analogs were neither antibacterial nor mutagenic. (no Refs)

CYTOGENETIC TESTS

20. IN VITRO IRRADIATION OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN G0 PHASE WITH 60CO GAMMA RAYS DID NOT INCREASE THE YIELD OF SISTER CHROMATID EXCHANGES.

Piatkin EK, Nugis VIu
No affiliation given
Radiobiologiia; 22(1):102-105 1982

The frequency of sister chromatid exchanges (SCE) was studied in cultured human peripheral blood lymphocytes irradiated with 60Co gamma rays (100, 200, 300, 400, and 500 rads) in G0 phase. Dosages tested for all radiation showed that the frequency of SCE in the test cultures did not differ from that in control. These findings indicate that SCE can not be used for dose indication during acute radiation injuries. (14 Refs) (In RUS)

21. QUANTITATIVE STUDIES ON BLEOMYCIN-INDUCED STRAND BREAKAGE OF CHROMATIN DNA.

Kataoka K
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Okayama Igakkai Zasshi; 93(3/4):361-381 1981

Single and double strand breakage of DNA by bleomycin under various conditions was analyzed quantitatively using purified simian virus 40 (SV40) DNA and SV40 chromatin. The method employed for DNA assay was fluorometry of SV40 DNA separated into three forms I, II, and III by 1.4% agarose gel electrophoresis and stained with ethidium bromide. This method was extremely simple and accurate for quantitative estimation of single and double strand breakage of circular DNA. The amount of bleomycin required for in vitro breakage of SV40 chromatin DNA was much higher than that of naked SV40 DNA. 2-Mercaptoethanol accelerated bleomycin-induced DNA strand breakage. The concentration of 2-mercaptoethanol required for the acceleration was higher in SV40 chromatin than in SV40 DNA. DNA strand breakage was induced by ferrous ions in the absence of bleomycin to a similar level in SV40 chromatin and in SV40 DNA. The acceleration of bleomycin-induced strand breakage by a low concentration of ferrous ion was higher in SV40 DNA than in SV40 chromatin. Ethylenediamine tetraacetic acid (EDTA) and copper ions were not efficient for stopping the reaction of bleomycin-induced DNA breakage. Sodium dodecyl sulfate (SDS) was a useful reagent for stopping the reaction. (Author abstract) (75 Refs) (In JPN)

22. EFFECT OF MALONALDEHYDE AND ACETALDEHYDE ON CULTURED MAMMALIAN CELLS. PRODUCTION OF MICRONUCLEI AND CHROMOSOMAL ABERRATIONS.

Bird RP, Draper HH, Basrur PK
Dept. Nutrition, Univ. Guelph, Guelph, Ontario N1G2W1, Canada
Mutat Res; 101(3):237-246 1982

The genotoxic effects of malonaldehyde (MA) and acetaldehyde (AA) were investigated using rat skin fibroblasts grown in primary culture. Production of micronuclei and aberrant chromosomes were used as indices of genotoxicity. Micronuclei were observed in cultures exposed to all concentrations of MA tested, this effect being concentration-dependent at least up to 10(-3) M. AA treatment also resulted in dose-dependent production of micronuclei, although higher concentrations were required. Treatment of the cells with MA at 10(-4) or 10(-3) M for 12 hr resulted in structural aberrations in the chromosomes, including acentric chromosomal fragments, achromatic lesions and chromatid breaks. In the case of AA, only 10(-3) M concentration produced an increase in metaphases with chromosomal aberrations. The effect of 10(-3) M AA was similar to that of 10(-4) M MA. Treatment with either aldehyde at either concentration resulted in a marked increase in the number of metaphases with structural and numerical aberrations. MA at all concentrations tested induced chromatid breaks, gaps, deletions and fragmentation. AA produced similar abnormalities but only at the higher concentration. (30 Refs)

23. MICRONUCLEI IN MOUSE BONE MARROW ERYTHROCYTES AFTER TREATMENT WITH RADIOPHOSPHORUS.

Olinici CD, Uray Z, Ban C, Dobay O
Dept. Morphopathology, Inst. Medicine and Pharmacy, Cluj-Napoca, Romania
Morphol Embryol (Bucur); 28(1):55-57 1982

The incidence of micronuclei in bone marrow RBC was studied in mice 30 days after ip administration of radiophosphorus (32P) in doses of 5, 10, 25, 50, 100 and 200 uCi. The incidence of micronuclei per 1,000 RBC in controls was 2.9. After 32P, incidences were 3.8 at 5 uCi to 105.4 at 200 uCi. There was a linear correlation between dose of 32P and the incidence of micronuclei after 30 days. The micronucleus test might thus be used for the biological dosimetry of internal radiation. (10 Refs)

24. ANAPHASE ABERRATIONS: A MEASURE OF GENOTOXICITY IN MUTAGEN-TREATED FISH CELLS.

Kocan RM, Landolt ML, Sabo KM
Dept. Pathology, SM-30, Univ. Washington, Seattle, WA, 98195
Environ Mutagen; 4(2):181-189 1982

A continuous culture line of rainbow trout gonad (RTG-2) cells was exposed to benzo(a)pyrene (BAP), 3-methylcholanthrene (3MC), anthracene, 1-naphthol, 9-aminoacridine (9AA), mitomycin C (mit-C), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). During exposure cells were examined for the presence of abnormalities in chromosome arrangement of anaphase figures during mitosis, and were compared to the effects of only solvent (dimethylsulfoxide). Both BAP and 3MC elevated the number of anaphase abnormalities, with more effect at 48 hr than at 24 hr. MNNG, mit-C, and 9AA were also effective in increasing the number of abnormalities. Abnormalities included mainly attached fragments, acentric fragments and bridges, with some side-arm bridges and multipolar cells. Toxicity and inhibition of cell division were also observed with all compounds. No increase in chromosomal lesions was observed in cells treated with naphthol or anthracene, suggesting that each chemical's characteristics, not the chemical class to which it belongs, are important in mutation induction. The in vitro RTG-2 cell system has a highly active mixed function oxygenase system, which eliminates the need for microsomal supplement. This test system is comparable to the Ames test and the sister-chromatid exchange test in sensitivity for measuring chromosome damage. (38 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

25. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTES FOLLOWING IN VIVO TREATMENT WITH DINITROTOLUENE.

Mirsalis JC, Butterworth BE
SRI International, Building 205, 333 Ravenswood Ave., Menlo Park, CA, 94025
Carcinogenesis; 3(3):241-245 1982

The purpose of this study was to examine the induction of unscheduled DNA synthesis (UDS) by the potent hepatocarcinogen technical grade dinitrotoluene (tgDNT; 76% 2,4-dinitrotolulene, 19% 2,6-dinitrotolulene) using the in vivo-in vitro hepatocyte DNA repair assay. Male Fischer-344 rats were treated by gavage and hepatocytes were isolated by liver perfusion and cultured with [3H]thymidine. UDS was measured by quantitative autoradiography as net grains/nucleus (NG); greater than or equal to NG was considered positive. Controls consistently had-3 to-6 NG. A dose-related increase in UDS was observed 12 hr after treatment, with 200 mg/kg tgDNT producing 26 NG. A 50-fold increase in the number of cells in S-phase was observed at 48 hr after treatment. This increase in S-phase cells could be suppressed in the presence of 10-20 mM hydroxyurea (HU), while the same levels of HU did not affect the level of UDS at 12 hr after treatment. 2,4-DNT produced only a weak response, in contrast to 2,6-DNT which was a potent inducer of UDS. Treatment of female rats with tgDNT yielded only modest increases in UDS and DNA replication relative to males. These results are consistent with the carcinogenicity studies and indicate that tgDNT is a potent genotoxic agent, with 2,6-DNT contributing the major portion of the effect. (Author abstract) (20 Refs)

26. THE FORMATION OF BENZO[A]PYRENE - DEOXYRIBONUCLEOSIDE ADDUCTS IN VIVO AND IN VITRO.

Ashurst SW, Cohen GM
(c/o Cohen) Toxicology Unit, Dept. Pharmacology, Sch. Pharmacy, Univ. London, 29/39 Brunswick Square, London, WC1N 1AX, England
Carcinogenesis; 3(3):267-273 1982

The formation of DNA-bound products from benzo[a]pyrene was studied using metabolic activation systems of widely differing cellular and structural integrity. The nature of the benzo[a]pyrene-metabolite-deoxyribonucleoside adducts formed was markedly dependent on the nature of the activation system used. Systems where cellular integrity is preserved, namely mouse skin in vivo and rat liver hepatocytes and lung explants in vitro, when treated with benzo[a]pyrene, formed deoxyribonucleoside adducts of which the major one co-chromatographed with a bay-region diol epoxide-deoxyguanosine adduct, 10beta-(deoxyguanosin-N2-yl)-7beta,8alpha,9alpha trihydroxy-7,8,9, 10-tetrahydrobenzo[a]pyrene. In striking contrast, the use of activating systems with disrupted cellular integrity such as rat liver, rat lung and mouse skin microsomal fractions, in the presence of benzo[a]pyrene and exogenous DNA, resulted in the formation of deoxyribonucleoside adducts derived predominantly from either a further metabolite of 9-hydroxybenzo[a]pyrene or (+-)benzo[a]pyrene-4,5-epoxide. The consequences of such results are important when considering the widespread use of subcellular fractions such as microsomes as metabolic activating systems for short-term mutagenicity and carcinogenicity tests. (Author abstract) (41 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

27. METABOLIC ACTIVATION OF 3-METHYLCHOLANTHRENE AND BENZO(A)PYRENE TO MUTAGENS IN THE L5178Y/TK ASSAY BY CULTURED EMBRYONIC RODENT CELLS.

Amacher DE, Paillet SC, Zelljadt I
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Environ Mutagen; 4(2):109-119 1982

Early passage cultured rodent cells [Crl;COBS CD(SD) BR rats, Crl;COBS CD1 (ICR) BR mice, Ela ENG/SYR hamsters] were used for the activation of 3-methylcholanthrene (3MCA) and benzo(a)pyrene (B(a)P) in the mouse lymphoma L5178Y/TK mutation assay. S9 mix prepared from cells of the same three rodent lines was used for comparison. Both B(a)P and 3MCA were mutagenic when tested with 5% (vol/vol) S9 from all three sources, but were negative in the L5178Y/TK mutation assay without S9. When tested with three different primary mouse embryo cultures B(a)P was negative, but 3MCA was reproducibly positive. Responses were similar with rat embryo cultures. Both B(a)P and 3MCA gave positive results with hamster embryo monolayers; for 3MCA the SHE X and SHE-48 sources were used. Cell contact between the lymphoma cells and the hamster cells was studied with the use inverted microscopes. A mutagenesis assay using intact hamster cells for the metabolic component and L5178Y cells as targets is evidently feasible. (34 Refs)

28. EFFECT OF DIETARY PROTEIN ON INDUCTION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE MUTAGENESIS BY RAT LIVER MICROSOMES IN THE SALMONELLA/MICROSOME TEST SYSTEM (MEETING ABSTRACT)

Singletary KW, Martin SE, Milner JA
Department of Food Science, University of Illinois, Urbana, IL, 61801
Fed Proc; 41(3):356 1982

Studies have shown that a high protein diet decreases the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors in rats. The present studies were designed to evaluate the influence of dietary protein on the ability of rat liver microsomes to mediate DMBA-induced mutagenesis. Female rats (150g) were fed isocaloric diets containing 7.5, 15.0 or 45.0% protein as casein for 2 weeks. All rats were treated with Aroclor (100mg/kg) 5 days before sacrifice. Liver homogenates (S-9) were prepared and evaluated for their influence on the mutagenicity of DMBA (20 g/plate) with Salmonella typhimurium TA98. S-9 fractions from rats fed the 7.5% protein diet produced approximately 100% more DMBA-induced revertants per mg protein than S-9 fractions from rats fed the 15 or 45% protein diets. Pair feeding studies revealed food intake did not account for these differences. The duration of feeding was also found to influence the S-9 activation effects of dietary protein. These results suggest that the Salmonella/microsome mutagenesis assay has potential use as a relatively simple and rapid system to evaluate the influence of dietary protein source and concentration as factors modifying carcinogenesis. (no Refs)

29. MICROSOMAL METABOLISM OF 8-FLUOROBENZO[A]PYRENE (MEETING ABSTRACT)

Chou MW
National Center for Toxicological Research, Jefferson, AR, 72079
Fed Proc; 41(3):1573 1982

Fluorobenzo[a]pyrene (8-FBP) is a more potent mutagen than benzo[a]pyrene (BP) in Salmonella typhimurium tester strain TA98 and TA1538 with S9 or microsome activation. Metabolism of 8-FBP by rat liver microsomes was studied to elucidate the activation pathways. The major metabolites formed were purified by high performance liquid chromatography and identified as 3-hydroxy-8-FBP, 3,x-dihydroxy-8-FBP and 8-FBP- trans-4,5-dihydrodiol by the analyses of uv, mass and nmr (nuclear magnetic resonance) spectra. The circular dichroism spectrum of 8-FBP-trans-4,5-dihydrodiol was similar to that of BP-4R,5R-dihydrodiol, a metabolite of BP, indicating that 8-FBP-trans-4,5-dihydrodiol also has a 4R,5R absolute configuration. The results suggest that a fluoro substituent at C-8 of BP (1) can inhibit the enzymatic oxidation at the 7,8-and 9,10-positions but (2) does not change the stereospecificities of the cytochrome P-450 enzymes and of epoxide hydrolase for 8-FBP-trans-4R,5R-dihydrodiol formation. The results also suggest that 8-FBP-4,5-oxide, the precursor of 8-FBP-trans-4,5-dihydrodiol, may be an ultimate mutagenic metabolite of 8-FBP. (no Refs)

COMPARATIVE TEST RESULTS

30. DNA DAMAGE IN LIVER, KIDNEY, BONE MARROW, AND SPLEEN OF RATS AND MICE TREATED WITH COMMERCIAL AND PURIFIED ANILINE AS DETERMINED BY ALKALINE ELUTION ASSAY AND SISTER CHROMATID EXCHANGE INDUCTION.

Parodi S, Pala M, Russo P, Zunino A, Balbi C, Albini A, Valerio F, Cimberle MR, Santi L
Dept. Oncology, Istituto Scientifico per lo Studio e la Cura dei Tumori, 16132 Genon, Italy
Cancer Res; 42(6):2277-2283 1982

Aniline of unknown purity has been reported to induce spleen hemangiosarcoma in rats. Aniline has been found to be negative in terms of mutagenicity in both bacteria and yeasts. We have found that both commercial (already rather pure) and repurified aniline are clearly positive to a similar extent in inducing DNA damage in vivo in liver and kidney of rats. Both the commercial and repurified product are also clearly positive in induction of sister chromatid exchanges in vivo in male Swiss mice bone marrow cells. Liver, kidney, and bone marrow DNA damage was absent in male Swiss mice. (Author abstract) (30 Refs)

31. COMPARISON OF THE MUTAGENIC POTENCY OF 2-CHLOROETHANOL, 2-BROMOETHANOL, 1,2-EPOXYBUTANE, EPICHLORHYDRIN AND GLYCIDALDEHYDE IN KLEBSIELLA PNEUMONIAE, DROSOPHILA MELANOGASTER AND L5178Y MOUSE LYMPHOMA CELLS.

Knaap AG, Voogd CE, Kramers PG
Natl. Inst. Public Health, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
Mutat Res; 101(3):199-208 1982

The mutagenic activities of a series of chemically related mutagens in the Klebsiella pneumoniae fluctuation test, in the sex-linked recessive lethal test in Drosophila melanogaster, and in the HGPRT forward mutation test in L5178Y mouse lymphoma cells were tested. Compounds investigated included 2-chloroethanol (CE), 2-bromoethanol (BE), 1,2-expoxybutane (EB), epichlorohydrin (ECH), and glycidaldehyde (GA). In the fluctuation test, increased mutation rates were observed at concentrations of 5 and 0.1 milliM (mM) for CE and BE, respectively. Among the epoxides, the lowest effective concentrations were 1.0, 0.1 and 0.01 mM for EB, ECH and GA, respectively. In the sex-linked recessive lethal test, CE and BE were not mutagenic. EB at concentrations of 117 and 233 mM significantly increased mutation frequency. ECH had been shown by others to be mutagenic in this system, a result which was verified here. GA significantly increased mutation frequency at concentrations of 25 mM and higher. In the HGPRT mutation assay, induction of mutations were observed after treatment with EB and ECH, with ECH being the more mutagenic of the two compounds. (23 Refs)

REVIEWS AND OTHER RELATED STUDIES

32. MUTAGENESIS VS CARCINOGENESIS.

Taylor SL
Food Res. Inst. Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI, 53706
Food Technol; 36(3):65-68,98,100,102-103,127 1982

Factors influencing the predictive value of mutagenicity tests for detecting carcinogens include the nature of the mutagenesis system; the population, identity, and nature of the chemicals being tested; the chemical classes of the compounds being tested; the reliability of the data; and the nature of any activating system that may be involved. Short-term mutagenicity tests may be useful for identifying food components that warrant further toxicologic evaluation and for studying the mechanism of carcinogenesis. They may eventually replace long-term carcinogenicity tests in animals; data generated by the present short-term tests, however, must be interpreted with caution. (65 Refs)

33. PRINCIPLES OF CANCER BIOLOGY: ETIOLOGY AND PREVENTION OF CANCER.

Upton AC

Dept. Environmental Medicine, New York Univ. Medical Center, New York, NY

Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Somatic mutation, aberrant differentiation, virus activation, and cell selection form the basis of contemporary theories of carcinogenesis. None of these theories accounts for all of the observed phenomena of neoplasia. Both initiating and promoting factors seem to be required for chemical carcinogenesis in humans. The development of sound safety standards and codes of practice are the best means of risk avoidance, but the development of these standards has often lagged behind the demonstration of carcinogenicity. The problems has been complicated by uncertainty and controversy about the criteria for the determination of the carcinogenicity of a given agent, and also for assessing the magnitude of the risk occurring in exposed populations. Workable interim approaches to the resolution of these problems have been developed. (194 Refs)

34. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.

Sugimura T

Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan

Cancer; 49(10):1970-1984 1982

Identification of mutagens, carcinogens, tumor promoters in human food is reviewed. Studies of the food additive 2-(2-furyl)-3-(5-nitrofuryl)acrylamide, which is mutagenic in the Ames test and produced tumors in mice, indicated that if a compound in food shows mutagenicity, its carcinogenicity should be considered and that data obtained on mutagenicity prior to 1960 may be invalid. Improvement and adoption of the Ames test for screening for carcinogens in food are discussed. Isolation and identification of new heterocyclic amines from pyrolysates of amino acids, proteins, and proteinous foods are described. Mutagens and carcinogens in edible plants, vegetables, fruits, alcoholic spirits, spices, and beverages are described. Tumor promoters are discussed in relation to life style. Recommendations are proposed for cancer prevention. (159 Refs)

35. ON THE NECESSITY OF MUTAGENICITY TESTING OF NEW DRUGS.

Bogajewski J, Schoneich J

Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland

Pol Tyg Lek; 37(2):63-67 1982

Studies on the importance of mutagenicity testing of new drugs and test methods are reviewed. Mutagenicity testing is also important for the detection of carcinogenic effects in view to the close correlation between mutagenic and carcinogenic properties of chemical substances. The test systems include Proteus mirabilis PG 273 and PG 713, Escherichia coli pol A+ and pol A-, Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100, TA 1959, TA 1952 and TA 1534, Chinese hamster SV 70, Ehrlich's ascites tumor cells, and murine bone marrow cells. (34 Refs) (In POL)

36. TESTS FOR ASSESSING THE MUTAGENIC ACTION OF DRUGS IN MAN.

Obe G, Madle S

Insitut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany

Prax Klin Pneumol; 35(Suppl1):1027-1033 1981

Cultures of human peripheral-blood lymphocytes are used for routine, rapid testing of mutagenicity. Lymphocytes are stimulated to undergo mitosis in vitro. Mitotic chromosomes are then examined for aberrations such as sister chromatid exchanges, dicentric chromosomes, and fragmentation. Findings are used to predict the effects of potential mutagens in humans. Problems of in vitro testing and alternative methods of testing are discussed. (17 Refs) (In GER)

37. MUTAGENESIS ASSAY METHODS.

Casciano DA

Div. Mutagenesis Res., Natl. Center Toxicological Res., FDA, Dept. Health and Human Services, Jefferson, AR, 72079

Food Technol; 36(3):48-50,52 1982

Submammalian, as well as several in vitro and in vivo mammalian mutagenesis assay systems currently being used or developed to detect potential mutagens or carcinogens are described and discussed, with particular regard to advantages and disadvantages of each system. Bacterial systems are most useful as prescreens to detect mutagens capable of inducing point mutations and to identify the type of lesion induced at the molecular level. They are inexpensive, rapid, and easily adapted to inclusion of exogenous metabolic activation systems, but they are not readily amenable to detection of chromosome aberrations and results are difficult to extrapolate to man. Uses, advantages, and disadvantages of in vitro mammalian systems are similar to those of submammalian systems, although the former have the advantage of having a mammalian genome as the target molecule. Use of the intact mammal in mutagenicity/carcinogenicity testing provides the closest approach to metabolic conditions in humans. These include the 'spot' test, micronucleus test, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal, heritable translocation, phenotypic specific locus, and biochemical specific locus. (18 Refs)

38. OCCURRENCE OF MUTAGENIC PRODUCTS IN BROWNING MODEL SYSTEMS.

Shibamoto T

Dept. Environmental Toxicology, Univ. California, Davis, CA, 95616

Food Technol; 36(3):59-62 1982

Studies suggest that some browning products may play a role in the mutagenicity of tars obtained from cooked foods. Browning model systems consisting of simple amines and carbonyls have been used to study the nature of cooked foods and can play an important role in the investigation of chemical mutagenicity and carcinogenicity. Results obtained from maltol/NH3 and rhamnose/NH3/H2S model systems are presented. Major components of browning reaction mixtures are nitrogen-containing compounds such as pyrazines and imidazoles. Some of these compounds are mutagenic in the Ames test, Saccharomyces cervisiae, or Chinese hamster ovary cells, indicating the necessity of further mutagenicity testing. (35 Refs)

39. THE CARCINOGENICITY OF N-NITROSO COMPOUNDS: A SIMCA PATTERN RECOGNITION STUDY.

Dunn WJ, Wold S
Dept. Medicinal Chemistry, Coll. Pharmacy, Univ. Illinois Medical Center, 833 S. Wood, Chicago, IL, 60612
Bioorg Chem; 10(1):29-45 1981

The SIMCA method of pattern recognition was used to estimate the carcinogenic potential (CP) of a number of N-nitroso compounds in the rat. With the SIMCA method, classification as a carcinogen or non-carcinogen is based on physicochemical descriptions (data) of the compound, with the mathematical regularity within the data for each class represented by a principal components model. Data were obtained from published animal studies in which nitrosamines, N-nitroso ureas, and N-nitroso urethans had been tested. The nitroso compounds were administered to rats either in drinking water or by gavage. CP was evaluated coincident with location of tumor induction. Comparison of known CP data with SIMCA results showed that 88% of active compounds were correctly classified. This method, while theoretically based, gives an estimate of CP similar to that in the Ames mutagenicity test. (18 Refs)

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CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
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OCTOBER, 1982

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TESTS FOR CELL TRANSFORMATION

1. CHEMICAL INTERACTIONS WITH HERPES SIMPLEX TYPE 2 VIRUS: ENHANCEMENT OF TRANSFORMATION BY HYDRAZINE AND 1,2-DIMETHYLHYDRAZINE.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT, 84602
Chem Biol Interact; 40(1):97-112 1982

Quantitative assays for the morphological transformation of 3T3 Swiss mouse cells by herpes simplex Type 2 virus (HSV-2) were employed to examine the effect on cell transformation of chemical carcinogens and suspected carcinogens. Exposure of the cells to the chemical compound, followed by virus infection, resulted in enhancement of transformation when compared to that observed with chemical or virus alone. Enhancement occurred in tests utilizing either UV light-inactivated HSV-2 (strain 333) or a temperature-sensitive (ts) mutant of HSV-2 [A8(293)]. A series of seven ts-mutants were tested and exhibited varying degrees of transformation. Enhancement of transformation occurred in cells treated with hydrazine (HZ) and 1,2-dimethylhydrazine (SDMH). No enhancement occurred when cells were treated with monomethylhydrazine,

HE 26. 3173/2:

1,1-dimethylhydrazine and the jet fuels JP-5, JP-10, RJ-4 and RJ-5. A strong time dependence after treatment was demonstrated with some enhancement seen at 6 hr after chemical treatment but the greatest enhancement appeared when virus infection began after 24 hr of chemical exposure. (Author abstract) (25 Refs)

2. INITIATION OF C3H/10T1/2 CELL TRANSFORMATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND AFLATOXIN B1.

Boreiko CJ, Ragan DL, Abernethy DJ, Frazelle JH
Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709
Carcinogenesis; 3(4):391-395 1982

The utility of C3H/10T1/2 mouse embryo fibroblasts for the detection of carcinogenic substances has been limited by their apparent insensitivity to the oncogenic effects of direct-acting alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and procarcinogens such as aflatoxin B1 (AfB1). Because the process of C3H/10T1/2 transformation can be observed to proceed through discrete stages of initiation and promotion, we have considered the possibility that MNNG and AfB1 may only initiate C3H/10T1/2 transformation. Treatment of asynchronous C3H/10T1/2 cells with MNNG or AfB1 alone generally produced few transformed foci. If MNNG or AfB1 treatment was followed by the exposure of cells to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), numerous transformed foci were produced. Phorbol did not enhance transformation by either substance. MNNG and AfB1 thus appear to be initiating agents for transformation. TPA also enhanced the transformation of C3H/10T1/2 cells by low doses of 3-methylcholanthrene (3-MCA), but transformation by high concentrations of 3-MCA was inhibited by the presence of TPA. These studies suggest that the sensitivity of the C3H/10T1/2 transformation system to potential carcinogens can be dramatically heightened if the bioassay is conducted in the presence and absence of TPA. (Author abstract) (37 Refs)

IN VIVO TESTS FOR MUTAGENICITY

3. MEETING REPORT: WORKSHOP ON THE PRACTICAL APPLICATION OF THE MAMMALIAN SPOT TEST IN ROUTINE MUTAGENICITY TESTING OF DRUGS AND OTHER CHEMICALS.

Braun R, Russell LB, Schoneich J
Zentralinstitut fur Genetik und Kulturpflanzenforschung der AdW der DDR, 4325 Gatersleben, E. Germany
Mutat Res; 97(2):155-161 1982

The mammalian spot test, which was developed in relation to radiation mutagenesis, is reviewed with respect to treatment procedure, spot classification, statistical evaluation, and interpretation of results. Variables regarding treatment include time, dose, and route of application. Spots resulting from expression of recessives (RS), from cell killing (WMVS), and spots due to misdifferentiation (MDS) are distinguishable by location and color, and must be recorded separately. The spots test is relatively fast compared with some other whole-mammal tests, but requires more resources than do assays involving prokaryotes, lower eukaryotes and cell-culture systems. Major strengths of the spot test are it is an in vivo test; it monitors gene mutation end-points, as well as several types of chromosomal damage; and it provides ancillary information on cytotoxicity, embryotoxicity and teratogenicity of a compound. A positive result classifies a chemical as a potential carcinogen; to date all agents found positive have been carcinogens or have not been tested for carcinogenicity. A positive spot test will also indicate the possibility that inherited damage could be produced, which would indicate further germ-line mutagenicity studies. A negative test must be qualified by the possibility of a placental barrier. (3 Refs)

4. IDENTIFICATION OF CARCINOGENS BY MEASUREMENT OF CELL-MEDIATED IMMUNITY: II. ASSAY SPECIFICITY.

Stevens RH, Cole DA

Dept. Radiology, Radiation Res. Lab., Univ. Iowa, Iowa City, IA, 52242

Environ Res; 28(1):67-76 1982

Studies utilizing the Fischer F334 inbred rat model were undertaken to define the specificity for antitumor cell-mediated immune (CMI) measurements as determined by lymphoid-cell cytotoxicity to determine whether such values could serve as an analytical reflection for the carcinogenic potential of environmental pollutants. The investigations revealed that specificity was apparently limited to a carcinogenic insult and designated by the embryonic origin of the affected tissue. For example, it was found that animals having x-ray-induced small-bowel, 1,2-dimethylhydrazine-induced colon, and 7,12-dimethylbenz[a]anthracene-induced pancreas adenocarcinomas possessed lymphoid cells cytotoxic to tumor target cells of either the small bowel or pancreas, but were not lytic to tumor tissue of ectodermal or mesodermal origin. Nor was injury inflicted upon normal intestinal, kidney, or tail fibroblastic cells, while significant lysis was seen when normal fetal cells were used as targets. The findings also suggest that the presence of the carcinogen in the assay has little influence upon the CMI values. Thus, the present investigation continues to support the concept that immunological responsiveness may serve as a useful measure for specifically identifying and quantitating effects of environmental carcinogens. (Author abstract) (23 Refs)

5. A NOTE ON THE UTILITY OF REPAIR-DEFICIENT ST MUS302 DROSOPHILA FEMALES IN DETECTING CHROMOSOME LOSS AND SEX-LINKED RECESSIVE LETHALS INDUCED IN THE MALE GENOME BY METHYL METHANESULFONATE (MMS) AND DIMETHYLNITROSAMINE (DMN).

Zimmering S

Div. Biology and Medicine, Brown Univ., Providence, RI, 02912

Environ Mutagen; 4(3):291-293 1982

A study is presented which indicates that for the monofunctional alkylating agents methyl methanesulfonate and dimethylnitrosamine, the st mus302 test for chromosome loss is more sensitive than the mei-9a or conventional test (using repair-proficient females). The test is as sensitive as a sex-linked recessive lethal test treating Basc males and mating with st mus302 females. (7 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

6. MUTAGENICITY OF METAL SALTS IN THE L5178Y MOUSE LYMPHOMA ASSAY.

Oberly TJ, Piper CE, McDonald DS
Biochemical Toxicology, Dept. Toxicology, Eli Lilly and Co., PO Box 708, Greenfield, IN, 46140
J Toxicol Environ Health; 9(3):367-376 1982

The potential of 11 metals to induce forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells was studied. Strong positive responses at survivals greater than 10% were observed with CdSO4, K2CrO4, K2Cr2O7, and MnCl2. Weak positive responses, yielding 2-3x increases in the mutation frequency above the solvent control and at greater than 10% survival, were seen with HgCl2, NaAsO2, Na2HAsO4, and Pb(NO3)2. Negative responses were obtained with MgCl2, NaCl, and AlCl3. Because many of the suspect carcinogens studied here are present in the cities atmosphere, nonurban areas, and industrial plants, a strict evaluation of their genetic or carcinogenic risk to humans is necessary. The mouse lymphoma TK+/- system should be valuable in identifying and quantitating the mutagenicity of this class of environmental agents. (22 Refs)

7. INVESTIGATIONS ON THE MUTAGENIC AND CLASTOGENIC ACTIVITY OF RESORCIN. CYTOGENETIC FINDINGS FROM DIFFERENT TYPES OF HUMAN CELLS.

Schulz R, Schwanitz G, Winterhoff H
(c/o Schwanitz) Institut fur Humangenetik, Universitat Bonn, Wilhelmstrasse 31, 5300 Bonn, W. Germany
Arzneim Forsch; 32(5):533-536 1982

The suspected clastogenic effect of m-dihydroxybenzene (resorcin), a phenol derivate, was investigated by analyzing three different types of human cells: (1) lymphocyte cultures from blood of healthy blood donors with normal karyotype (46, XY); (2) lymphocyte cultures from patients with a proven chromosome abnormality (trisomy 21, karyotype: 47, +21); and (3) cultures of amniotic cells with normal karyotype (46,XX and 46,XY). In all three cell systems resorcin induces secondary chromosome aberrations. The number of cells with aberrations increases with the concentration of the substance and duration of action. The three cell systems tested showed a different sensibility to resorcin. Lymphocytes with trisomy 21 were more sensitive than the same cell type with a normal karyotype. Both types of lymphocytes were less sensitive to resorcin than amniotic cells. The types of structural chromosome aberrations observed in these investigations as well as the concentration of the test substance, which had to be added to induce a clastogenic effect, demonstrated that resorcin has to be regarded as a weak mutagenic substance. (Author abstract) (16 Refs) (In GER)

8. NEUROBLAST OF THE GRASSHOPPER EMBRYO AS A NEW MUTAGEN TEST SYSTEM. II. CHROMOSOME BREAKAGE INDUCED BY IN VITRO EXPOSURE OF EMBRYOS TO THE DIRECT-ACTING MUTAGENS 4NQO, MMNG, ADRIAMYCIN, AND BLEOMYCIN.

Liang JC, Gaulden ME
(c/o Gaulden) Radiation Biology Section, Dept. Biology, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235
Environ Mutagen; 4(3):279-290 1982

Embryos of the grasshopper Chortophaga viridifasciata (De Geer) were used in a new mutagen test system at a stage equivalent to 14-day development at room temperature. Embryos were separated from yolk and put in 35 mm x 10 mm plastic petri dishes which contained 5 ml of Mark's M-20 culture medium with 7.5% fetal calf serum plus antibiotics. Adriamycin (ADM) and bleomycin (BLM) were added to the medium directly; 4-nitroquinoline-1-oxide (4NQO) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were dissolved in dimethyl sulfoxide (DMSO). The dose response for the induction of acentric chromosome fragments was determined in neuroblasts of the embryos exposed in vitro to the four direct-acting chemicals, which are known to be mutagenic. After 1-hr exposure followed by a 3-hr recovery period (untreated cell cycle time is 4 hr) acentric fragments were observed at doses down to 1.0 uM 4NQO, 1.25 uM MNNG, and 0.125 uM ADM and BLM. With 4NQO, acentric fragments were induced at a dose as low as 0.125 uM after 8-hr continuous exposure. No chromosome aberrations or mitotic effects were observed in untreated embryos or those exposed only to DMSO. Comparison with other clastogen test systems currently used indicate that the grasshopper neuroblast test is the fastest and that it detects some agents that some other systems do not. (40 Refs)

MICROBIAL TESTS FOR MUTAGENICITY

9. ESTIMATING THE PROPORTION OF MUTAGENIC COMPOUNDS IN ENVIRONMENTAL SAMPLES.

Rao BR, Janardan KG, Schaeffer DJ

(c/o Schaeffer) Illinois Environmental Protection Agency, 2200 Churchill Road, Springfield, IL, 62706

J Toxicol Environ Health; 9(3):499-508 1982

An approach for estimating the proportion of mutagens in a sample of N compounds was developed, based on discrete contagious distribution theory. A formula (not based on the normal distribution) for the correlation between the numbers of mutagens and nonmutagens in a sample was also developed. Estimates of the proportions of compounds tested and mutagenic activity, and untested but mutagenic were developed from the existing compilations, and a high, statistically significant correlation between the total number of mutagens in a sample and the sample size N is shown. (12 Refs)

10. MUTAGENICITY OF THREE AROMATIC AMINES IN THE PRESENCE OF FRACTIONS FROM VARIOUS TISSUES.

Fouarge M, Mercier M, Poncelet F

Laboratoire de Toxicologie et Bromatologie, UCL-72.37, Sch. Pharmacy, Avenue E. Mounier 72, B-1200 Brussels, Belgium

Toxicol Lett; 11(3/4):313-320 1982

Salmonella typhimurium strain TA-1538 was used as a test system for mutagenicity studies of 2-aminofluorene (2-AF), 4-aminobiphenyl (4-ABP) and 3,2'-dimethylaminobiphenyl in the presence of post-mitochondrial fractions (liver, kidney, intestine, colon, testicle) of untreated and pretreated rats. The highest mutagenic activity was detected with 2-AF and the lowest with 4-ABP. Activating capacity of liver post-mitochondrial fraction was highest, followed in order by kidney, testicle, intestine, and colon. No relationship was found between the mutagenic activity and the carcinogenicity of the compounds. (20 Refs)

11. METABOLIC ASPECTS OF THE COMUTAGENIC ACTION OF NORHARMAN.

Sugimura T, Nagao M, Wakabayashi K
Natl. Cancer Center Res. Inst., Tsukiji, Chuo-Ku, Tokyo, Japan
Adv Exp Med Biol; 136(partB):1011-1025 1982

Microbial mutagenicity tests were conducted using norharman (beta-carboline) in the Ames Salmonella typhimurium assay with strain TA 98. Comutagenicity of norharman with aniline was demonstrated, and linear dose-response curves were obtained with the aniline metabolites phenylhydroxylamine and nitrosobenzene in the presence of 200 ug norharman. Norharman was comutagenic with o-toluidine, but not with m- or p-toluidines. It induced mutagenesis in yellow OB dye, but not red dye number 2, which does not yield either aniline or o-toluidine upon hydrolysis. 3-Aminopyridine and 2-amino-3-methyl-pyridine were mutagenic in the presence of norharman, but eight other aminopyridine derivatives were not. Diphenylnitrosamine (DPhN) and diphenylamine (DPhA) were mutagenic in the presence of norharman and S-9 mix, but not without both added components in the incubation medium. Mutagenicity of DPhN seems to be due to DPhA formed metabolically. Other strains of S typhimurium (TA 1538, TA 1978) showed sensitivity to aniline + norharman, and strains TA 100 and TA 1535 were totally unaffected. A mixture of microsomes + supernatant + NADPH yielded more revertants than microsomes alone, microsomes + NADPH, or supernatant + NADPH. (41 Refs)

12. OPTIMUM S9 CONCENTRATIONS IN BACTERIAL MUTAGENICITY ASSAYS.

Forster R, Green MH, Priestley A
Water Res. Centre, Medmenham Marlow, Bucks, England
Adv Exp Med Biol; 136(partB):1263-1269 1982

Activation of 2-acetylaminofluorene (AAF) in two assay systems using bacterial mutagenesis is discussed. A modified incubation mixture was prepared, containing soft agar, which was dispensed to either Ames test (AT) plates or fluctuation test (FT) replicate tubes. Results indicate that the soft agar and temperature change cause some loss of activity and have a slight effect on the S9 optimum compared with a conventional FT. The S9 optimum of the modified FT could be compared with the response in a conventional FT. The S9 optimum is altered in the modified test and resembles a characteristic AT response. The same result was obtained when purified microsomes were used for activation instead of S9-mix indicating that the diffusion of cytosolic constituents of S9 fraction is not responsible for the difference. The concentrations of NADPH and NADPH generating system do not influence the S9 optimum. The diffusing factor was investigated by the addition of a number of agents to FT incubate. The presence of corn oil increased and broadened the S9 optimum suggesting that the agent is lipophilic. The addition of DNA (57 ug/ml), protein (2.5 mg/ml bovine serum albumin), or glutathione (2.5 mg/ml), and uridine diphosphate glucuronic acid (250 ug/ml) did not affect the S9 optimum. The effects of two ring hydroxylated AAF metabolites on the activation of AAF were examined in an AT. While the 1-OH metabolite had a slight inhibitory effect on AAF activation, the 7-hydroxy metabolite had a stimulatory effect on AAF activation. Results suggest that feedback effects of relatively unreactive metabolite of AAF may offer a mechanism for the apparent diffusible inhibition of microsomal activation but if so the action of the metabolite must be complex. (4 Refs)

13. EFFECTS OF PLATING EFFICIENCY AND LOWERED CONCENTRATION OF SALTS ON MUTAGENICITY ASSAYS WITH AMES' SALMONELLA STRAINS.

Witmer C, Cooper K, Kelly J
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Adv Exp Med Biol; 136(partB):1271-1284 1982

Effects of altering the concentrations of total salts and histidine on number of spontaneous revertants, survival rates for the auxotrophic strains of bacteria, response to chromium(VI) (Cr VI) as a mutagen, and response to sodium azide (SA) as a mutagen in a standard Ames test (SAT) were studied. TA 100 which responds to both frame-shift and base-pair mutagens, and/or TA 1535 which detects base-pair mutagens only were used. For strains TA 100 and TA 1535 the actual numbers of spontaneous revertants that appeared after 48 hr of incubation varied as a function of the number of bacteria plated rather than appearing to be constant. The large numbers of isolated colonies appearing after 48 hr incubation when less than 10(4) bacteria were plated on the his+ minimal agar with conditions identical to those described for TA 100 and TA 1535 are shown. Most strains tested survived poorly with lowered salts available and apparent survival was dependent on both the histidine and salts concentrations. The apparent low survival rates of all strains tested except for TA 1535 on the 1/3 (S) plates after 48 hr of incubation with 0.045 milliMoles histidine are presented. The surviving colonies when the plates were reincubated and recounted at 72 hr are shown as well as the apparent percentage survival of five strains in a typical series of experiments. An example of the use of lowered concentrations of salts in detecting mutagenicity of Cr VI compounds is presented. Results with SA indicated that decreased concentration of salts resulted in decreased response to SA as a mutagen. Results indicated that some inorganic compounds can be more accurately detected as mutagens using modified conditions of SAT. (11 Refs)

14. DETECTION OF MUTAGENIC/CARCINOGENIC ACTIVITY IN WATER WITH THE SALMONELLA/ MICROSOME TEST (AMES TEST).

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GWF Wasser Abwasser; 123(1):39-41 1982

The use of Salmonella and microsomes in the Ames test to detect mutagenic or carcinogenic substances in water is reviewed. Mutagenicity is measured by counting the number of bacteria that revert from histidine-dependence to histidine-independence. The Ames test is suitable only for testing alkylating agents. Because mutagenicity indicates only a probability of carcinogenicity rather than a certainty, the Ames test cannot be used as a final test of carcinogenicity. The procedure is appropriate to screen compounds found in water for further testing. (16 Refs) (In GER)

15. MUTAGENICITY TEST WITH IMMOBILIZED MICROORGANISMS.

Fontani F
No affiliation given
Not Chim Farm; 21(1):36-37 1982

New method for the mutagenicity testing of chemical substances using Rec- and Rec+ strains of Bacillus subtilis immobilized on membranes attached to oxygen electrodes is described. The current of the Rec- electrode increases in the presence of mutagenic substances in proportion to their concentrations in the solution. The Rec+ strain is able to repair DNA damage caused by mutagenic substances. (no Refs) (In ITA)

16. MICROBIAL DETECTION OF MUTAGENIC NITRO-ORGANIC COMPOUNDS IN FILTRATES OF COAL FLY ASH.

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Environ Mutagen; 4(3):249-258 1982

The Ames Salmonella test, as measured by his+ revertants, was used to determine whether nitro-organic compounds may be the direct-acting mutagens present in previously reported mutagenic coal fly ash samples. Tester strains (TA 100, TA 1538, TA 98) and their respective nitroreductase (NR)-deficient mutants (TA 100 nr, TA 1538 nr, TA 98 nr1, and TA 98 nr2) were used to test mutagenicity of coal fly ash extracts prepared with horse serum, dimethyl sulfoxide, or an azeotropic benzene/methanol mixture. 2-Nitrofluorene was used as a positive control to assess the responsiveness of the four NR-deficient strains. Addition of S-9 fraction significantly increased mutagenic activities of the ash extracts. The data were normalized to net revertants/10(8) S typhimurium cells/mg ash used. Both four-way and three-way analyses of variance were used to simultaneously evaluate differences between solvent extracts, fly ash mutagen, S-9 activation, and NR-deficient strains and their parental strains. The benzene/methanol azeotropic mixture generally had the highest extraction power, horse serum the lowest. The results show that overall 87.5% (+-1.8 standard error of the mean) of the mutagenic activity was associated with the nitro-organic compounds. (15 Refs)

TESTS FOR DNA DAMAGE AND REPAIR

17. DISSOCIATED OCCURRENCE OF SINGLE-GENE MUTATION AND ONCOGENIC TRANSFORMATION IN C3H 10T1/2 CELLS EXPOSED TO ULTRAVIOLET LIGHT AND CAFFEINE.

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J Cell Physiol; 111(3):309-314 1982

Effects of caffeine and UV light on postreplication repair were studied in C3H mouse embryo-derived 10T1/2 cell clones between passages 11-15. Alkaline sucrose gradient sedimentation experiments showed that the DNA synthesized by 10T1/2 cells after UV irradiation was of reduced mol wt when compared to parental DNA. When cells were exposed to 1 milliM caffeine after UV irradiation the DNA repair was severely inhibited. Results indicated that caffeine potentiated the killing of 10T1/2 cells by UV light. Caffeine was effective in enhancing cell killing at all UV doses tested although the differential effects between 0.5 and 1 milliM were less pronounced at higher UV doses. With UV doses of 5 and 10 Joule/square meter (J/m2), the addition of caffeine resulted in higher transformation frequencies. The rate of increase at two UV doses were 2.4- and 2.3-fold/milliM caffeine, respectively. When the transformation of unirradiated cells exposed to caffeine for 48 hr was measured, caffeine alone induced transformation. However, the transformation potentiation effect of 1 milliM caffeine after 10 J/m2 was statistically significant. The potentiation factor was 1.7. Caffeine by itself did not induce detectable ouabain-resistant mutations in 10T1/2 cells; a possible inhibitory effect was observed. Results indicate that gene mutation and malignant transformation in 10T1/2 cells can be dissociated. (45 Refs)

18. ISOLATION OF UV-SENSITIVE MUTANTS OF MOUSE L5178Y CELLS BY A CELL SUSPENSION SPOTTING METHOD.

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Somatic Cell Genet; 8(3):329-345 1982

A new method is described for isolation of UV-sensitive mutants, which is applicable to cell lines growing in suspension, and which yields greater than 90% of highly UV-sensitive mutants. It is also useful in complementation assay. Fifty-six UV-sensitive mutants of L51 T/t mouse cells were isolated by the cell suspension spotting procedure after treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5, 1.0, or 1.5 ug/ml for 2 hr) or ethylmethane sulfonate (400 or 600 ug/ml for 18 hr). Mutagen-induced frequencies for highly UV-sensitive mutants were about 2-3x higher than those of 6-thioguanine-resistant (hypoxanthine phosphoribosyltransferase-negative) mutants. Four UV-sensitive mutants belonging to different complementation groups were examined for their sensitivity to killing by UV, 4-nitroquinoline-1-oxide, (4NQO) mitomycin C (CMMC), x-rays and MNNG. All four mutants were cross-sensitive to UV, 4NQO, and MMC, but not to x-rays, indicating that the cross-sensitivity might consist of at least four complementation groups. The method described is applicable to recovering more repair-deficient mouse cell mutants for studies of repair mechanisms. (47 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

19. DIFFERENTIAL ABILITY OF AMBYSTOMA TIGRINUM HEPATIC MICROSOMES TO PRODUCE MUTAGENIC METABOLITES FROM POLYCYCLIC AROMATIC HYDROCARBONS AND AROMATIC AMINES.

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Sloan Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY, 10580
Cancer Lett; 16(1):33-41 1982

The ability of salamander hepatic microsomal mixed function oxygenases to metabolize benzo(a)pyrene (BP), perylene and the aromatic amines 2-aminoanthracene (AA), 2-aminofluorene (AF), 2-acetylaminofluorene (AAF), 4-amino-trans-stilbene (AS), monoacetylbenzidene (MAB), and diacetylbenzidine (DAB), to chemical species capable of inducing revertants in Salmonella typhimurium was investigated. Microsomal enzyme preparations from the livers of Aroclor-induced salamanders mediated the activation of AA, AF, AAF, AS, MAB, and DAB. Benzidene and 4-aminobiphenyl were poorly mutagenic in this system. The reactions were NADPH- and microsomal enzyme concentration-dependent. Rat microsomal enzyme induction with phenobarbital produced a marked increased in mutagenesis by benzidine, MAB, and DAB. However, phenobarbital was not a more effective inducer than Aroclor in the activation of these or other tested aromatic amines by salamander enzymes. No evidence was observed that BP or perylene were mutagenic after reaction with salamander liver microsomes. It is suggested that amphibian microsomal oxygenases may carry out N-oxidation more efficiently than C-oxidation. (30 Refs)

20. MUTAGENICITY OF TRANS-ANETHOLE, ESTRAGOLE, EUGENOL, AND SAFROLE IN THE AMES SALMONELLA TYPHIMURIUM ASSAY.

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Bull Environ Contam Toxicol; 28(6):647-654 1982

The mutagenic activities of safrole, anethole, and eugenol in Salmonella typhimurium were investigated using the Ames method as well as the effect of incorporation of 3'-phosphoadenosine-5'-phosphosulfate (PAPS). The increase of revertant colonies as a result of incorporating PAPS into the microsomal, but not into the direct bacterial assay, suggested that safrole and related compounds may be converted to DNA binding sulfuric acid esters under the applied conditions. Incorporation of proper cofactors and soluble enzymes in vitro mutagenicity screens was important for optimization of the mutagenic response. (17 Refs)

21. COMPARISON OF MICROSOMAL INDUCER PRETREATMENT ON THE IN VITRO ALPHAHYDROXYLATION AND MUTAGENICITY OF N-NITROSOPYRROLIDINE IN RAT AND HAMSTER LIVER.

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Environ Mutagen; 4(3):221-230 1982

Reasonable agreement is demonstrated between rates of microsomal alpha-hydroxylation of N-nitrosopyrrolidine (NPYR) and the metabolic activation of NPYR to a mutagen by post-mitochondrial supernatants when changes in microsomal protein are taken into account. The Ames assay for mutagenicity was employed with use of Salmonella typhimurium strain TA 1535. Rats and hamsters were pretreated with 3-methylcholanthrene (MC), phenobarbital (PB) or Aroclor 1254 (AR). In the rat, most active post-mitochondrial supernatant preparations were obtained with PB and AR while in hamsters AR was most effective in increasing mutagenicity of NPYR. The influence of the various modifiers of mixed function oxidase activity on protein content was determined on liver subfractions. In the rat, no difference was observed in the protein content of post-mitochondrial or post-microsomal supernatant while all the inducers increased these parameters in the hamster. The same pretreatments were tested on the rate of microsomal alpha-hydroxylation of NPYR. In the rat, only AR pretreatment resulted in significant enhancement, while MC slightly decreased the rate. In the hamster, both MC and AR pretreatment markedly increased the rate. When NPYR alpha-hydroxylase is expressed per g of wet wt of liver, differences in the amount of microsomal protein are included and better agreement between metabolism and mutagenicity in PB pretreated animals is obtained. MC and AR pretreatment increased aldehyde dehydrogenase activity in post microsomal supernatants in both rats and hamsters, while PB only increased the activity in hamster preparations. (26 Refs)

COMPARATIVE TEST RESULTS

22. DETECTION OF MUTAGENIC ACTIVITY IN HUMAN URINE FOLLOWING FRIED PORK OR BACON MEALS.

Baker R, Arlauskas A, Bonin A, Angus D

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Cancer Lett; 16(1):81-89 1982

The mutagenic activity of urine from nonsmoking individuals following meals of fried pork and bacon was tested in the Salmonella typhimurium revertant assay. The greatest degree of mutagenicity was observed in urine collected 2-4 hr after ingesting the fried test foods. Evidence of mutagenic activity continued for up to 24 hr. In contrast, ingestion of microwave prepared pork products failed to produce urinary mutagens. Urine mutagenicity was unrelated to histidine concentration in urine because of the requirement for S9. Beta-glucuronidase did not enhance the activity of urine mutagens either when incorporated together with urine extracts in agar overlays, when preincubated with urine extract, or with various whole urine specimens. Mutagenicity was acetone extractable from fried but not from microwave-prepared or raw pork, and was associated with the basic fraction rather than the acidic plus neutral fraction. Activity was best detected in strains TA1538 and TA98. Liver S9 was required to detect mutagenicity in these meat extracts. Mutagenic extracts also increased the frequency of sex-linked recessive mutations in Drosophila melanogaster. (19 Refs)

23. EFFECTS OF CHLORINATED PARAFFINS ON SOME DRUG-METABOLIZING ENZYMES IN RAT LIVER AND IN THE AMES TEST.

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Adv Exp Med Biol; 136(partA):821-828 1982

Influence of chlorinated paraffins (CP) on induction of drug-metabolizing enzymes in rat liver and mutagenic effect in the Ames test are discussed. Results of induction of drug-metabolizing enzymes in rat liver by CP are presented. The liver-somatic index increased and the amount of cytochrome P-450 was not changed. The activity of microsomal epoxide hydrolase was not affected by treatment with Cereclor 42, but the activity increased 30, 90, and 200-330% after treatment with Cereclor S58, 70, and 70L, respectively. SDS-polyacrylamide gel electrophoresis was performed to compare the proteins of liver microsomes from control and induced rats. The same polypeptide pattern was observed in both groups of animals and some of the bands were increased in the treated rats. No toxic effects were noted in any of the strains in the Ames test and no differences in the number of revertants with the strains TA 1537 and TA 100 were observed. Strain TA 98 showed a slight increase in the number of revertants in the presence of S-9 fraction. This low increase may have arisen by chance since no dose related effects were observed with Cereclor 70L. Furthermore the lack of toxic effects may indicate that paraffin does not penetrate into bacterial cells. Possible modes of metabolism of Cereclor 70L include dechlorination and oxidation of the carbon chain. Metabolism of CP may also be related to their ability to induce epoxide hydrolase and glutathione S-transferase. (16 Refs)

24. MUTAGENIC ACTIVITY OF THREE ISOMERIC N-NITROSO-N-METHYLAMINO-PYRIDINES TOWARDS ESCHERICHIA COLI K-12 IN IN VITRO AND ANIMAL-MEDIATED ASSAYS.

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Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, The Netherlands
Carcinogenesis; 3(4):415-421 1982

Three isomeric nitrosomethylaminopyridines were tested in vitro and in the host-mediated assay for their activity to induce gene mutations in E coli K-12 strain 343/113. Nitrosodimethylamine (NDMA) and nitrosomethylaniline (NMA) were also tested. The in vitro mutagenicity tests were performed either without or in the presence of various fractions (S-9, microsomes, S-100) of rodent liver homogenates. The in vivo mutagenicity was determined in host-mediated assays, in which the indicator E coli cells were recovered for the liver of treated animals. N-nitro-N-methyl-2-aminopyridine (2-NMPY) and N-nitro-N-methyl-4-aminopyridine (4-NMPY) were activated to mutagenic factors by microsomes, but their mutagenic effect was completely abolished when S-100 was added. N-nitro-N-methyl-3-aminopyridine (3-NMPY) was directly mutagenic for E coli but its mutagenic potential was abolished when S-100 liver fraction was added to the incubation mixtures. NDMA was activated to mutagenic factors with both microsomes and S-9 fractions, whereas NMA could not be shown as mutagenically active under any of the present experimental conditions. It could be shown that the deactivating effect of the S-100 fraction was of non-enzymatic nature, and probably was due to the presence of thiol-containing 'scavenger' molecules in this fraction. In the host-mediated assays, only the 2-isomer among the three exerted a mutagenic affect. The results indicate that the isomers investigated here are mutagenic either directly or upon microsomal activation. The non-carcinogenicity of 3-NMPY and 4-NMPY, and the non-mutagenicity of these compounds in host-mediated assays, is probably the result of very efficient deactivation by cytosolic (thiol-group-containing?) factors. (23 Refs)

25. CARCINOGENICITY OF FLUOROCARBONS: ASSESSMENT BY SHORT-TERM IN VITRO TESTS AND CHRONIC EXPOSURE IN RATS (MEETING ABSTRACT)

Longstaff E, Robinson M, Bradbrook C, Styles JA, Purchase IF
Central Toxicology Laboratory, Alderley Park, N. Macclesfield, Cheshire, England
Toxicologist; 2(1):106 1982

Twenty-one fluorocarbons were evaluated for mutagenic activity using Salmonella typhimurium. Twelve of these were also assessed in the BHK21 cell transformation assay. Monochlorodifluoromethane (FC-22), chlorofluoromethane (FC-31), 1-chloro-1,1-difluoroethane (FC-142b), 1,1-difluoro-2-chloroethane (FC-142) and 1,1,1-trifluoroethane (FC-143a), showed mutagenic activity towards Salmonella and FC-31 and FC-142b were positive in the BHK21 test. The in vivo carcinogenicity of some of these chemicals was also assessed by a long-term bioassay. Wistar rats (40/sex/group) were dosed by gavage with 300 mg/kg bodyweight of 3% w/v in corn oil FC-22, FC-31, FC-133a (2-chloro-1,1,1-trifluoroethane), FC-134a (1,1,1,2-tetrafluoroethane) and FC-143a, five days a week for one year. One undosed and two dosed control groups were employed. The study was terminated at 126 wks. Rats dosed with FC-31 showed a high incidence of stomach squamous cell carcinomas and fibrosarcomas. Female rats dosed with FC-133a had a markedly increased incidence of uterine adenocarcinomas while the males of the group had a greatly increased incidence of testicular interstitial cell tumors and all had marked testicular atrophy. Carcinogenicity was not seen with any of the other fluorocarbons. (no Refs)

26. MAMMALIAN CELL POINT MUTATION ASSAY WITH THE ANTINEOPLASTIC AMSACRINE (MEETING ABSTRACT)

Lake RS, McGuire EJ, De la Iglesia FA

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Toxicologist; 2(1):173 1982

A battery of short-term in vitro tests was designed for evaluating carcinogenesis potential of the antineoplastic agent amsacrine, an acridinylamino anisidine derivative. Previous genotoxicity assays showed frameshift mutagenesis at the hisC3076 locus in Salmonella TA-1537 but no confirmed mutagenesis in TA-98, TA-100, TA-1535, and TA-1538. In Chinese hamster ovary cell assays, amsacrine induced sister-chromatid exchanges and hyperdiploid chromosomes. There are no data available on mammalian point mutation with amsacrine and a V-79 Chinese hamster lung cells assay was conducted to detect HGPRT (hypoxanthine guanine-phosphoribosyltransferase) locus mutation. Cytotoxicity was established at 2 ug/ml and one hour exposures were used with 2, 1, 0.5 and 0.25 ug drug/ml in duplicate flasks. Positive control was ethylmethane sulfonate at 800 ug/ml. Lethality occurred at 2 and 1 ug/ml. A significant number of 6-thioguanine resistant mutant colonies were induced at 0.5 and 0.25 ug/ml. The results indicate high mutagen sensitivity of this assay when compared to the dose required to induce reverse mutation in prokaryotes with a 1,000-fold separation in minimum effective dose. The evaluation of the battery of tests conducted unequivocally render a genotoxic potential. (no Refs)

27. GENOTOXICITY EVALUATION OF AMSACRINE (MEETING ABSTRACT)

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Toxicologist; 2(1):175 1982

Acridinylamino derivatives constitute compounds with antineoplastic properties. Comparative genotoxicity and hence carcinogenic potential of 4'-(9-acridinylamino) methanesulphon-m-anisidide (amsacrine) was studied in several bacterial and mammalian cell in vitro assays. In a Salmonella plate incorporation assay, reverse mutation was observed only at 269 ug/plate in the nonactivation phase in frameshift tester strain TA-1537. In a preincubation modification of this assay, significantly increased revertant counts were obtained in TA-1537, TA-1535, and TA-100 at a cytotoxic dose of 672 ug/plate without S9. In the presence of S9, mutagenic activity was manifest only with TA-1537, indicating that potential base substitution activity of amsacrine was prevented more readily than its frameshift activity specific for TA-1537. At these high cytotoxic doses, a significant portion of presumed revertants did not grow in histidine-deficient medium and could have represented phenocopies. By contrast, doses as low as 0.02 ug/ml in culture medium without S9 induced a greater than five-fold increase in sister-chromatid exchange (SCE) rate and chromosomal damage frequency in Chinese hamster ovary cells in vitro. SCE response was more sensitive to S9 detoxification than the chromosomal aberration frequency. (no Refs)

28. MUTAGENICITY OF N-NITROSO BILE ACID CONJUGATES IN SALMONELLA TYPHIMURIUM AND DIPLOID HUMAN LYMPHOBLASTS.

Puju S, Shuker DE, Bishop WW, Falchuk KR, Tannenbaum SR, Thilly WG
(c/o Tannenbaum) Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Res; 42(7):2601-2604 1982

Two N-nitroso bile acid conjugates, N-nitrosotaurocholic acid and N-nitrosoglycocholic acid, were tested for mutagenicity by forward mutation assay in Salmonella typhimurium TM 677 and in diploid human lymphoblasts, line TK6. N-Nitrosoglycocholic acid and N-nitrosotaurocholic acid showed similar concentration-response curves in the bacterial assay with statistically significant mutant fractions observed at about 0.12 mM. Non-nitrosated parent compounds were nonmutagenic. However, in the human cell assay, N-nitrosotaurocholic acid gave statistically significant mutant fractions only at 0.4 mM, but N-nitrosoglycocholic acid was mutagenic at 0.05 uM, some 9,000x more potent. Experiments with quantitative Ames' S typhimurium reversion assays indicated mutagenesis via base substitution. (Author abstract) (11 Refs)

29. SISTER CHROMATID EXCHANGE RESPONSE OF HUMAN DIPLOID FIBROBLASTS AND CHINESE HAMSTER OVARY CELLS TO DIMETHYLNITROSAMINE AND BENZO(A)PYRENE.

Tomkins DJ, Kwok SE, Douglas GR, Biggs D
Dept. Pediatrics, McMaster Univ. Health Sciences Centre, Hamilton, Ontario L8N 3Z5, Canada
Environ Mutagen; 4(3):203-214 1982

A study was undertaken to examine the possibility that Chinese hamster ovary (CHO) and human diploid fibroblasts may not show the same sensitivity to well known carcinogens benzo(a)pyrene (BP) and dimethylnitrosamine (DMN), using a metabolic activation system and sister chromatid exchange (SCE) analysis. Metabolic activation in the tests was accomplished with a microsomal fraction from rats induced with Aroclor 1254. The human diploid lines employed were IMR-90, WI-8, and S-3299. For both BP and DMN the human cells and CHO cells showed dose-response slopes that were significantly different from zero, except for CHO cells treated with BP for 1 hr and S-3299 cells treated with DMN. While the responses of the human and CHO cells to BP, and the responses of the human cells to BP and DMN were similar, the dose-response of the human cells to DMN was statistically less significant than that of CHO cells. Reducing the period of treatment of CHO cells from 1.0 hr to 0.5 hr had no effect on the slope of the dose-response curves for BP and DMN. The observed differences between human and CHO cells may reflect differences in the fate of metabolic intermediates of DMN. (38 Refs)

30. MITHRAMYCIN- AND TRIETHYLENE MELAMINE-INDUCED SPERM ABNORMALITIES IN LAKEVIEW HAMSTERS.

Singh H, Newton D
Sch. Sciences and Technology, P.O. Box 20425, Savannah, GA, 31404
Environ Mutagen; 4(3):231-237 1982

The chemical sensitivity of the spermatogenic cell types to two mutagens and results are compared with similar studies in the mouse. Groups of an inbred PD4 strain of Charles Lakeview hamsters received sublethal doses of 0.01-0.25 mg/kg of triethylene melamine (TEM) or mithramycin (MR) in five daily ip injections. Testis weights, epididymal sperm numbers, and body weights were monitored 1, 4, and 10 wk after treatment. In TEM-treated hamsters sperm abnormalities were increased 8-fold whereas MR treatment increased abnormalities 21-fold (25% vs 1.2%). Frequency and type of aberrant sperm varied with dose and time, being most frequent at 1 and 4 wk with both agents. Both agents led to depressed sperm numbers and testis weights from weeks 4 to 10. Body weights of treated animals remained within 28% of control during the test period. While the findings were in general agreement with those found for mouse, the magnitude of the response and the stage of spermatogenic sensitivity in the chemical induction of sperm abnormalities in the two species were different. (22 Refs)

31. INDUCTION OF CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES BY RADIOMIMETIC SUBSTANCES (BLEOMYCIN AND PHLEOMYCIN) (MEETING ABSTRACT).

Scheid W, Traut H

Institut fur Strahlenbiologie, Universitat Munster, Munster, W. Germany

Molecular and Cellular Mechanisms of Irradiation, March 17-19, 1982, Neuherburg, W. Germany. Gesellschaft fur Strahlen und Umweltforschung MBH 65 pp., 1982.

The antibiotics bleomycin (BLM) and phleomycin (PLM) belong to the very small number of chemical substances which, like ionizing radiation, in addition to chromatid aberrations, induce chromosome aberrations as well. We investigated the induction of chromosome aberrations (dicentric chromosomes, ring chromosomes) in human lymphocytes by BLM and PLM. The av number of dicentric chromosomes per cell was 1.057 (BLM) and 1.273 (PLM). The concentrations (300 ug/ml) and exposure time (3 h) were the same in both series. The BLM-value obtained by Dresp et al for the same concentration is somewhat lower (0.420). In agreement with the results of the BLM studies of Dresp et al, the observed intercellular distribution of dicentric chromosomes in both the BLM and PLM series deviates from chance distribution (Poisson) ('overdispersion'). The proper chance distributions for both these distributions as well as for the distributions obtained by Dresp et al (several BLM concentrations) were calculated. In every case the same characteristic pattern was produced for the deviations of the observed frequencies from the theoretical. This 'deviation pattern' can in principle be interpreted in 2 different ways: (1) the BLM (PLM) molecules are randomly distributed on the cells, each molecule, however, tends to induce more than 1 aberration similar to the effects of dense ionizing particles. The linear relationship between aberration frequency and BLM concentration obtained by Dresp et al are in accordance with this conception. (2) The lymphocytes treated with BLM (PLM) consist of at least 2 subpopulations with different sensitivity with respect to the induction of chromosome aberrations. Such differences in sensitivity would however exist only for chemical noxae and not for ionizing radiation, since chance intercellular distribution of x-ray induced aberrations has been reported by different authors. Our results are at variance with mutagenicity studies in Drosophila in which BLM proved quite active and PLM, on the other hand, completely inactive. This demonstrates how important it is to perform mutagenicity testing with the most varied test systems possible. (no Refs) (In GER)

REVIEWS AND OTHER RELATED STUDIES

32. DETECTION OF POTENTIAL CARCINOGENS. GENETIC AND EPIGENETIC TESTS.

Devoret R
No affiliation given
C R Seances Acad Sci [Suppl]; (9):LXXXV-LXXXVI 1981

In view of the large number of potentially carcinogenic chemicals, long term tests to detect cancer, medium duration tests to detect cell transformation, and short term tests to detect DNA lesions have been developed. Short term tests are less costly and are reproducible and fast. Bacterial tests, lysogeny induction, and hypotheses related to neoplastic transformation are described. (no Refs) (In FRE)

33. DETECTION OF CARCINOGENIC EXPOSURES BY URINALYSIS: INDUCTION OF CELL-MEDIATED IMMUNITY.

Stevens RH, Cole DA
Radiation Res. Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA, 52242
Toxicol Lett; 11(3/4):299-303 1982

The colon carcinogen 1,2,-dimethylhydrazine (DMH: 0.1 to greater than 10 mg/kg) was administered sc to male Fisher F344 inbred rats; urine was collected over a 24 hr period and injected ip into a group of normal unexposed rats. DMH and its metabolites were excreted within 15 min in the urine and nearly 65% metabolized over a 24-hr interval. Cell mediated immunity (CMI) was measured by killing/injury of cultured x-ray induced rat small bowel adenocarcinoma target cells by peripheral blood lymphoid cells of urine-exposed animals. CMI was increased by urine collected from DMH exposed rats; a dose-response curve relationship was found, suggesting the presence of mutagenic/carcinogenic components. Although the actual DMH concentration in the urine was not known, it was less than 10(-4) times LD50 (1 g/kg) and 10(-3) times the amount necessary for tumor induction over a 20-mo latency period. This method has potential as a rapid non-invasive technique for screening individuals exposed to carcinogens. (15 Refs)

34. CONSTITUTIVE AND CARCINOGEN-DERIVED DNA BINDING AS A BASIS FOR THE ASSESSMENT OF POTENCY OF CHEMICAL CARCINOGENS.

Lutz WK
Inst. Toxicology, ETH, Univ. Zurich, CH-8603 Schwerzenbach, Switzerland
Adv Exp Med Biol; 136(partB):1349-1365 1982

The hypothesis that ground-level DNA damage is unavoidable and must be regarded as constitutive to a cell is presented. Sources for this type of damage include physiological reactive intermediates, nitrosamines, irradiation, carcinogenic metals, and viruses. Carcinogens are classified as initiating (DNA damaging, genotoxic) and nongenotoxic (act by modulating reactions and side reactions that increase or constitutive DNA damage or enhance the chance for such damage to proceed to a tumor). Carcinogenic potency of a carcinogen is defined as a product of persistent DNA damage x mutagenicity x nongenotoxic modulation of DNA damage. A correlation of DNA binding in vivo and the form of a 'Covalent Binding Index' (CBI) to the carcinogenic potency is shown. The CBI equals (micromole chemical bound/mole DNA nucleotides)/(millimole chemical administered/kg animal wt). Good linear correlation was found with an approx uncertainty of the estimate of a factor of 10 with a total span of values of 10(6). DNA binding is not enough to describe the potency of carcinogens; additional information is necessary to assess the organ specificity of initiating carcinogens. When administered alone, the nongenotoxic carcinogens appear to be much less potent than initiating carcinogens. Nongenotoxic carcinogens cannot be detected on the basis of chemical structure and short-term tests of their carcinogenic potency are not available. (21 Refs)

35. SYSTEMATIC CARCINOGEN TESTING THROUGH THE DECISION POINT APPROACH.

Williams GM, Weisburger JH
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Annu Rev Pharmacol Toxicol; 21:393-416 1981

The decision point approach for systematic evaluation of the potential hazards of chemicals is discussed. This approach is designed to yield a stepwise progression of data acquisition, and takes carcinogens into account in two ways: (1) a battery of short-term tests is constructed in an effort to include systems that may respond to epigenetic as well as genotoxic carcinogens, and (2) it is recognized that all forms of subchronic testing may fail to detect chemicals that can induce tumors in animals under specific conditions upon chronic administration. Other elements of the decision point approach are the use of a battery of short-term tests that may either eliminate the need for further testing or may enable verification of carcinogenic potential in one of four limited in vivo bioassays for carcinogenicity. (99 Refs)

36. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM
Frederick Cancer Research Center, Frederick, MD
Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

Chronic 2 year and lifetime rodent carcinogenesis bioassys have often been used to identify 'carcinogens'. Such identifications are purely phenomenologically based on statistically significant increased incidences of a specific tumor type or types. Many of these tumors, such as liver cell tumors in mice and rats and lymphomas in mice are normally found in high incidences in control animals. Routine chronic bioassays can only identify an increased incidence of a tumor type, and are not designed to reveal possible mechanisms(s) of induction of those tumors. In the past 10 years short term in vivo initiation-promotion assays have been developed which can identify chemicals as initiators, promotors or both for skin, liver and other tissues in rodents. Our review will outline the most effective methods for identification of a chemical as a carcinogen, promotor or other type of modifier of carcinogenesis. Examples will be given for cases where chemicals were identified as 'carcinogens' after routine chronic rodent bioassays but as promotors only after a subsequent short term initiation-promotion assay. A classification of rodent liver carcinogens and promoters will be given. Implications of these findings for regulatory purposes and the limited data base from which decisions on tumor promotors must be derived will be discussed. (no Refs)

37. INTERACTION OF SAFETY EVALUATION AND GOVERNMENT REGULATIONS (MEETING ABSTRACT)

Kolbye AC
Food and Drug Administration, Washington, DC, 20204
International Conference on Safety Evaluation and Regulation, of Chemicals, February 24-26, 1982, Boston, Massachusetts Bio-Research Institute; 1982

Dr Kolbye will discuss the shortcomings of short-term tests, the problems in defining relevant endpoints for both carcinogenesis and heritable genetic damage and will provide a perspective for the societal needs for improvements in food safety legislation and regulatory practice. Dr Kolbye speaks from the viewpoint of both medicine and law with over 12 years experience in FDA and over 20 years experience with the US government. (no Refs)

38. NEW APPROACHES TO CARCINOGEN BIOASSAY (MEETING ABSTRACT)

Williams GM
Naylor Dana Institute for Disease Prevention, Valhalla, New York
International Conference on Safety Evaluation and Regulation, of Chemicals, February 24-26, 1982, Boston, Massachusetts Bio-Research Institute; 1982

New knowledge on the mechanisms of action of chemical carcinogens and the validation of alternate approaches to chronic bioassay now permit rapid and reliable identification of carcinogens. As a guide to the systematic evaluation of chemicals, a 'decision point approach' was proposed, consisting of 5 sequential stages as follows: (a) structure activity considerations; (b) battery of in vitro short-term tests; (c) limited in vivo bioassays; (d) chronic bioassay; (e) final evaluation. Consideration of structure is directed toward anticipating the outcome of metabolic biotransformation, the generation of an electrophilic reactant, and the target sites for nongenotoxic effects. A reliable battery of five in vitro short-term tests can provide definitive evidence of genotoxic effects, permitting conclusion of testing. If the evidence of genotoxicity is equivocal or further confirmation is deemed necessary, four limited in vivo bioassays are available. Each of these can be used to detect genotoxic carcinogens as well as promoting agents. Chronic bioassay is reserved for compounds whose carcinogenic properties cannot be determined at the preceding stages of testing and where potential human exposure requires rigorous testing. The final evaluation is made only after sequential testing up to the stage required to provide definitive evidence or carcinogenicity or noncarcinogenicity. (no Refs)

39. THE ROLE OF SHORT-TERM MUTAGENICITY TESTS IN THE IDENTIFICATION OF HAZARDOUS CHEMICALS.

Zeiger E
Natl. Inst. Environmental Health Sciences, Box 12233, Research Triangle Park, NC, 27709
Tappi; 65(5):163-166 1982

Various short-term mutagenicity tests are described along with uses in determining mutagens in industrial processes, in effluents, and in body fluids. These tests must be evaluated in terms of potency and hazard assessment. The apparent high mutagenicity/carcinogenicity correlation presented by these tests is an oversimplification and may be misleading, and that different chemical classes show different levels of correlation. (8 Refs)

40. SCIENTIFIC CONSIDERATIONS IN MONITORING AND EVALUATING TOXICOLOGICAL RESEARCH.

Gralla EJ
Chemical Industry Inst. Technology, Research Triangle Park, NC
Scientific Considerations in Monitoring and Evaluating Toxicological Research. Washington, D. C., Hemisphere Publishing Corporation, 221 pp., 1981.

Evaluation, monitoring, and controlling the quality of complex biomedical and toxicological research studies, particularly those dealing with the toxic hazards of chemicals, are reviewed. The design and objectives of protocol preparation; quality assurance for rodents used in toxicological research and testing; generating and controlling atmospheres in inhalation chambers; quality assurance in the clinical laboratory; quality assurance in pathology; spontaneous lesions of importance for long-term toxicity testing in rats and mice; statistics and toxicology; data collection, record keeping, and reporting results; monitoring methods and problems in aquatic and wildlife toxicology; predictive assays for mutagens and carcinogens; monitoring problems in teratology; and some contractural and legal aspects of toxicological research are discussed. The semi-independent operation of specialists working within the same framework of responsibility creates an overlapping of professional interest in such fields as chemical safety evaluation, carcinogenesis, aquatic and wildlife toxicology, behavioral toxicology, veterinary toxicology, and regulatory toxicology. (330 Refs)

41. PREDICTIVE ASSAYS FOR MUTAGENS AND CARCINOGENS.

Butterworth BE
Chemical Industry Inst. Technology, Research Triangle Park, NC
Scientific Considerations in Monitoring and Evaluating Toxicological Research. Gralla EJ, ed. Washington, D. C., Hemisphere Publishing Corporation, 221 pp., 1981.

General principles involved in the formulation of a testing program for mutagens and carcinogens and the evaluation of results are presented. Considerations in the selection of systems and evaluation of results are outlined for bacterial mutagenesis assays, mammalian cell culture mutagenesis assay, cell transformation assays, DNA damage assays, DNA repair assays, and whole-animal systems including classical cytogenetic techniques, sister chromatid exchange assays, dominant lethal assay, sperm morphology assay, and the recessive spot test. (22 Refs)

42. RECENT RESEARCH ON ENVIRONMENTAL MUTAGENS - PARTICULARLY CARCINOGENIC AND PROTECTIVE FACTORS IN FOODSTUFFS AND RECOVERY FROM DNA DAMAGE IN HUMANS.

Kada T
Dept. Induced Mutation, Natl. Inst. Genetics, Mishima 411, Japan
Nippon Nogeikagaku Kaishi; 55(7):597-605 1981

Toxicity of mutagens, methods of detecting mutagens, inhibition of and protection from mutagens, and relationships of production and repair of DNA damage in humans and mammals with induction of spontaneous mutation are discussed. Toxicity of mutagens may take the form of carcinogenicity, aging, or genetic toxicity. Methods used to test and detect mutagenicity of substances includes the Rec-assay, the Ames test, the SD test, and a combination of the Rec-assay test as prescreening followed by the Ames test. Research on inhibition and protection from mutagens has focused on desmutagens and antimutagens. Research on production and repair of DNA damage in humans and mammals as related to induction of spontaneous mutation has focused upon PA enzyme activity, loss of DNA repair in ataxia, and inducing spontaneous mutations by fetal hamster cells. (43 Refs) (In JPN)

43. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H
Lab. Government Chemist, London, England
IARC Sci Publ (40): 347 pp., 1981.

Analysis of industrial and non-industrial aromatic amines (AA) and azo dyes (AD) is reviewed. AA and AD are considered with respect to biological activity (carcinogencity of AA and AD and their role in the development of human cancer, metabolic activation of AD), occurrence and monitoring in industry (biological monitoring of AA and their metabolites using short-term tests for carcinogenicity, AA of major industrial importance, survey of technics for estimating and monitoring AA of major industrial importance), AA and dyes in non-industrial exposures (mutagenic heterocyclic amines in cooked food; survey of the analysis of 2-acetylaminofluorene; overview of the toxicity, metabolism, and analysis of phenacetin; food colors), methods of analysis for AA and dyes in foods (analysis of 2-acetylaminofluorene in animal feed by spectrophotofluorescence, identification of water-soluble colors in food using paper and thin-layer chromatography, extraction of water-soluble colors from food using polyamide columns). (667 Refs)

44. ELIMINATION OF METABOLIC CO-OPERATION AND THE INDUCTION OF SISTER CHROMATID EXCHANGES ARE NOT PROPERTIES COMMON TO ALL PROMOTING OR CO-CARCINOGENIC AGENTS.

Kinsella AR
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England
Carcinogenesis; 3(5):499-503 1982

High densities of wild-type, 6-thioguanine sensitive V79 cells reduce the recovery of 6-thioguanine resistant (6TGR) cells when they are co-cultivated. This metabolic cooperation effect has been reported previously to be eliminated by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate and the accompanying enhancement of 6TGR colony recovery has been postulated as a rapid assay for tumor promoters. Elimination of metabolic cooperation, however, does not appear to be a characteristic of either the promoting agents anthralin, iodoacetic acid, oleic acid and delta-hemolysin or the co-carcinogenic/carcinogenic agents griseofulvin, diethylstilbestrol and stilbestrol diproprionate. Moreover, with exception of stilbestrol diproprionate, none of these agents induce sister chromatid exchanges, but are all, with the exception of delta-hemolysin, associated with limited numerical chromosome changes and in four cases low level aberration induction. None of the agents were mutagenic. (Author abstract) (53 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.
Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.
Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982
In ITA

6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.
Bishun NP
Tissue Culture and Cytogenetics Unit, Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England
J Surg Oncol; 20(2):115-118 1982

7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.
Raithel HJ, Schaller KH
Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany
Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
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8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.
Goldin A
Div. Cancer Treatment, NCI NIH, Building 37, Room 5E20, Bethesda, MD, 20205
INSERM Symp; 19:3-11 1981

9. PATHOLOGY.
Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

RADIATION CARCINOGENESIS

10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
Dreyer NA, Friedlander E
Epidemiology Resources, Inc., P.O. Box 57, Chestnut Hill, MA, 02167
Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.
Jankowski J
Instytut Medycyny Pracy w Lodzi, ul. Olowiana 6, 91-614 Lodz, Poland
Pol Przegl Radiol; 45(6):383-386 1981
In POL

12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)
Rossi HH
Columbia University, New York, NY
IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.
Law MP
MRC Cyclotron Unit, Hammersmith Hosp., London W12 OHS, England
Adv Radiat Biol; 9:37-73 1981

14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.
Granstein RD, Sober AJ
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
Proc Soc Exp Biol Med; 170(2):115-125 1982

15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.
Kalistratova VS
No affiliation given
Med Radiol (Mosk); 27(4):62-71 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

16. CAFFEINE: AN UPDATE.
Oser BL, Ford RA
Bernard L. Oser and Associates, 108-18 Queens Blvd., Forest Hills, NY, 11375
Drug Chem Toxicol; 4(4):311-329 1981

17. ANALYSIS OF MUTAGENIC EFFECTS OF FOREIGN SUBSTANCES IN THE FOOD PRODUCTS.
Maganova NB
Inst. Nutrition, Moscow, USSR
Vopr Pitan; (2):3-8 1982
In RUS

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

18. RADIATION EPIDEMIOLOGY (MEETING ABSTRACT)
Marks S
No affiliation given
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

19. EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION.
Fabrikant JI
Donner Lab., Univ. California, Berkeley, CA, 94720
Yale J Biol Med; 54(6):457-469 1981

20. EPIDEMIOLOGIC APPROACH TO CANCER.
Guinee VF
Dept. Epidemiology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

21. EPIDEMIOLOGY AND EARLY DETECTION OF CANCER OF THE ESOPHAGUS.
Sorouri P
900 Hillside Road, Wilmington, DE, 19807
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

22. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.
Hill MJ
Central Public Health Lab., Colindale Ave., London NW9, England
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Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
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24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)
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Preventive and Internal Medicine, Mayo Clinic, Rochester, MN
Eleventh Annual William Beaumont Gastrointestinal Symposium, March 24-26, 1982, El Paso, Texas. William Beaumont Army Medical Center 56 pp., 1982.

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Bayless TM, Yardley JH
Johns Hopkins Hosp., Baltimore, MD, 21205
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26. GENETIC ASPECTS OF GUT CANCER.
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27. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.
Nettesheim P, Topping DC, Jamasbi R
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Annu Rev Pharmacol Toxicol; 21:133-163 1981

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28. A SEARCH FOR SAFE DRINKING WATER.
Hairsine MA, Schumm HA
Northern Indiana Health Systems Agency, Inc., South Bend, IN
A Search for Safe Drinking Water. Available from National Technical Information Service, Springfield, VA, as HRP-0903845/6:, 68 pp., 1981.

29. OCCUPATIONAL EXPOSURES TO URANIUM: PROCESSES, HAZARDS, AND REGULATIONS.
Stoetzel GA, Fisher DR, McCormack WD, Hoenes GR, Marks S
Battelle Pacific Northwest Lab., Richland, WA
Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01:, 91 pp., 1981.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.
Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.
Svoboda DJ, Reddy J
Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.
Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

33. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.
Tew KD
Lombardi Cancer Center, Div. Medical Oncology, Georgetown Univ., 3800 Reservoir Road, N.W., Washington, DC, 20007
INSERM Symp; 19:61-77 1981

34. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS.
Ludlum DB, Tong WP
Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208
INSERM Symp; 19:21-31 1981

35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.
Veigl ML, Sedwick WD, Vanaman TC
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Fed Proc; 41(7):2283-2288 1982

36. METABOLISM AND TOXICITY OF AFLATOXINS.
Hsieh DP, Wong JJ
Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616
Adv Exp Med Biol; 136(partB):847-863 1982

37. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.
Lenk W, Scharmer U
Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Adv Exp Med Biol; 136(partB):951-970 1982

38. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

Henschler D, Hoos R

Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9,
Wurzburg D-8700, W. Germany

Adv Exp Med Biol; 136(partA):659-666 1982

39. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas
Medical Branch, Galveston, TX

Adv Exp Med Biol; 136(partA):693-701 1982

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300
RA Leiden, The Netherlands

Adv Exp Med Biol; 136(partA):809-820 1982

41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ.
Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W.
Germany

Hepatogastroenterology; 28(4):221-228 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ,
England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine,
Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

In JPN

45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800
Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences,
Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

48. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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SHORT-TERM TEST SYSTEMS FOR CARCINOGENICITY AND MUTAGENICITY

SERIES CK19 No. 82/11

NOVEMBER, 1982

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TESTS FOR CELL TRANSFORMATION

1. MOLECULAR INTERACTIONS OF HIGH ENERGY FUELS AND JET FUELS WITH ONCOGENIC VIRUSES AND ENDOGENOUS VIRUSES.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Molecular Interactions of High Energy Fuels and Jet Fuels with Oncogenic Viruses and Endogenous Viruses. Available from National Technical Information Service, Springfield, VA, as N82-18855:, 110 pp., 1981.

The objectives of this research are to develop rapid in-vitro assays to evaluate the carcinogenic potential of chemicals used by the US Air Force. Snyder-Theilen feline sarcoma virus (ST FeSV), quantitatively transforms human skin fibroblasts following second order kinetics. These studies were performed in order to determine whether chemicals altered ST FeSV transformation in a predictable manner and to correlate the alteration with the carcinogenic or non-carcinogenic activity of the test chemical. The results, to date, show diverse carcinogens classed as: aromatic amines, polycyclic hydrocarbons. Aminofluorenes, hydrazines, asbestos and mycotoxins inhibited virus transformation when virus infected cells (2 hr post-infection)

HE 20. 3173/2:

were exposed to test chemical, while non-carcinogenic chemicals had no significant effect on transformation. Triton X-100, acetone, petroleum and shale oil derived JP5; RJ5 and diesel fuel, marine, demonstrated non-carcinogenic activity while formaline demonstrated carcinogenic activity. Experiments designed to show the specificity of the antagonistic effect of known carcinogens are reported. Disulfuram inhibits biotransformation of 1,2 symmetrical dimethyl hydrazine (SDMH) metabolites, azomethane to azoxymethane (ultimate carcinogen) thereby preventing carcinogenic effect of the proximate carcinogen SDMH. Detailed methodology required to ascertain effect of chemicals on ST FeSV pro-virus integration and synthesis are presented. (Author abstract)

IN VIVO TESTS FOR MUTAGENICITY

2. A SCHEDULE TO DEMONSTRATE RADIATION-INDUCED SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES.

Chaudhuri JP
Laboratorium fur Experimentelle Radiologie, D-8042 Neuherberg bei Munchen, W. Germany
Radiat Environ Biophys; 20(3):223-229 1982

In view of the known poor response of sister chromatid exchange (SCE) to radiation, a schedule was developed involving the use of caffeine to demonstrate radiation-induced SCE. Other variables included control of the volume of medium, phytohemagglutinin stimulation, and bromodeoxyuridine treatment. With the use of this schedule, a dose-dependent increase in the frequency of radiation-induced SCE was observed. (31 Refs)

3. CHOLINE-LIPOTROPE DEFICIENT (CLD) DIET AS A MITOGENIC SUBSTITUTE FOR PARTIAL HEPATECTOMY (PH) IN THE INDUCTION OF RESISTANT HEPATOCYTES BY CARCINOGENS AS A SHORT TERM IN VIVO TEST (MEETING ABSTRACT).

Ghoshal AK
University of Toronto, Toronto, Ontario M5S 1A8, Canada
Proc Am Assoc Cancer Res; 23:379 1982

Induction of resistant hepatocytes is a property of many carcinogens useful as an end-point in a short term in vivo test. Cell proliferation is essential for this effect. With non-necrogenic carcinogens, PH has been used as mitogen. CLD diet has been shown to induce liver cell proliferation. Fischer rats were fed CLD diet for one wk, then injected with single or divided doses of 1,2-dimethylhydrazine (DMH) (100 mg/kg), benzo(a)pyrene (B(a)P) (200 mg/kg) or DL-ethionine (E) (50 mg/100 g BW) and the deficient diet continued for an additional week. After a two wk period on a standard basal diet with choline, the animals were assayed for foci of resistant hepatocytes by the Solt-Farber procedure using dietary 2-AAF plus PH with gamma-glutamyl transferase (gamma-GT) as the histochemical marker. B(a)P and DMH each induced 12 foci/cm2 and E 9, as compared to O-2 with CLD diet alone. Since the CLD diet is associated with hepatocyte proliferation for at least one wk, it now becomes possible to use divided doses or even continuous brief exposure to a possible carcinogen to increase the sensitivity of the assay. The use of the CLD diet facilitates the testing of many possible carcinogens by this procedure. (3 Refs)

4. THE STABILITY AND REGRESSION OF DENA INITIATED FOCI BY PHENOBARBITAL (MEETING ABSTRACT).

Herren SL, Pereira M, Britt AL, Khoury MM
U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Proc Am Assoc Cancer Res; 23:376 1982

An initiation/promotion bioassay in rat liver using gamma-glutamyltranspeptidase (GGTase)-positive foci as the endpoint has been developed to determine the carcinogenic potential of chemicals and environmental samples. These foci are presumed to be precancerous lesions. In an experiment to determine the stability and regression of GGTase-positive foci over time, rats received a 2/3 partial hepatectomy followed 24 hr later by diethylnitrosamine (DENA; 0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for 8 wk. After 8 wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number and area of GGTase-positive foci present in the liver were determined at various time points after DENA administration. The number of foci/cm2 in the rats taken off phenobarbital promotion initially decreased; although by 56 wk it approached the number present in the rats on continuous promotion. The size of the foci at 56 wk was larger in the rats on continuous promotion. After 81 wk, all 6 of the rats on continuous promotion had liver tumors while only 3 of 6 rats removed from promotion after 8 wk had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the size of DENA initiated foci as well as the ultimate incidence of liver tumors. (no Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

5. L5178Y TK +/- MOUSE LYMPHOMA CELL MUTAGENESIS ASSAYS OF 40 CODED COMPOUNDS (MEETING ABSTRACT).

Rudd CJ, Mitchell AD, Myhr BC, Caspary WJ, Poulton S, Lee YJ
SRI International, Menlo Park, CA, 94025
In Vitro; 18(3,part2):299 1982

The L5178Y TK +/- mouse lymphoma mutagenesis assay system is being validated by two laboratories using a common protocol to test coded compounds. Results have been obtained for 40 compounds representing members of 24 chemical classes. The results include the toxicity and mutagenicity of the compounds tested in both the presence and absence of a rat liver metabolic activation system. Experiments which met criteria for acceptable limits of toxicity and spontaneous mutation frequencies were used to evaluate each chemical's mutagenic response, and 98% agreement has been obtained between the laboratories. These results are compared with the results of testing the same compounds in other laboratories by other in vitro and in vivo approaches for the National Toxicology Program. Thus far, only four compounds, benz(a)anthracene, benzo(a)pyrene, calcium chromate, and 4-nitroquinoline-N-oxide, were positive in each type of assay; none was consistently negative. (no Refs)

6. MUTAGENICITY OF CARCINOGENS IN CULTURED HUMAN EPITHELIAL CELLS (MEETING ABSTRACT).

Allen-Hoffmann BL, Connell ND, O'Connell T, Rheinwald JG
Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Assoc Cancer Res; 23:364 1982

Most human cancers arise from epithelial cells. Difficulty in growing these cells has impeded study of the relationship between chemically induced mutation and carcinogenic alterations in human epithelial cells. We used X-rays, N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG), and 7,12-dimethyl benzanthracene (DMBA) to induce mutations in the hypoxanthine-guanine phosphoribosyl-transferase locus (HPRT) of human keratinocytes. Mutant cells were selected by resistance to 6-thioguanine (TG). In order to measure mutation in feeder layer-dependent human epithelial cells a TGr clone of the Swiss mouse fibroblast line 3T3 (3T3M1) was isolated. With 3T3M1 it is possible to select HPRT- epithelial cells while fulfilling their feeder layer requirement. Using this modified system we report the first successful selection of mutant human epithelial cells. A near-diploid human squamous cell carcinoma line, SCC-13y, and normal diploid human keratinocytes were used to select for induced mutations. HPRT- keratinocytes from Lesch-Nyhan patients were used to optimize selection conditions for normal human keratinocytes whereas a spontaneous mutant of SCC-13y was used to determine optimal expression time, population density and TG concentration for the carcinoma line. Mutagens increased the incidence of mutants 50-to 70-fold. Mutant colonies from a DMBA-treated population of SCC-13y were aminopterin-sensitive and possessed no HPRT activity. Selection of induced mutants from normal human keratinocytes and mesothelial cells is in progress. (no Refs)

7. QUANTITATION OF SMALL COLONY TRIFLUOROTHYMIDINE-RESISTANT MUTANTS OF L5178Y/TK+/- MOUSE LYMPHOMA CELLS IN RPMI-1640 MEDIUM.

Moore MM, Howard BE
Mutagenesis and Cellular Toxicology Branch, Genetic Toxicology Div. (MD68), United States Environmental Protection Agency, Research Triangle Park, NC, 27711
Mutat Res; 104(4/5):287-294 1982

Detection and quantification of thymidine kinase (TK)-deficient sigma mutants were studied in RPMI-1640 medium with and without heat inactivation and in heat-inactivated Fischer's medium. Neither the frequency nor the relative proportion of sigma and lambda TK-deficient methyl methanesulfonate-induced mutants was significantly affected by any of the media conditions tested. Because of the difficulty in quantitating spontaneous sigma mutant frequency in unheated RPMI-1640, however, Fischer's medium is thought to provide a cleaner selection of sigma spontaneous mutants in the L5178/TK+/- assay. (14 Refs)

8. MUTATION ASSAY AT THE THYMIDINE KINASE LOCUS IN DIPLOID HUMAN LYMPHOBLASTS.

Liber HL, Thilly WG
(c/o Thilly) Genetic Toxicology Group, Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Mutat Res; 94(2):467-485 1982

Characterization of a thymidine kinase (TK) mutation assay was studied in WI-L2 human lymphoblasts and the response of the system to a variety of chemical mutagens is reported. The TK6 cell line could be mutated from TK+/- to TK-/- state by ethyl methanesulfonate, butyl methanesulfonate, nitrosomethylurea, UV light, ICR-191, 4-nitroquinoline oxide, fluorodeoxyuridine, benzo[a]pyrene, and aflatoxin B1, and was derived from HH4. TK6 contains approx 30% of the TK enzyme activity of the parent. (26 Refs)

9. A THREE-TIER SCREEN, FOR GENOTOXIC CHEMICALS, USING V79 CHINESE HAMSTER CELLS (MEETING ABSTRACT).

Peterson AR, Uwaifo A, Peterson H
Cancer Research Laboratory, University of Southern California Cancer Center, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:367 1982

Measurements of mutagenesis to 8-azaguanine-(AG)-resistance, cytotoxicity and DNA synthesis inhibition in V79 Chinese hamster cells have been developed for use as criteria for assessing the genotoxicity of chemicals. The measurements were made in cells that had been treated for 2 hr with chemicals known to be genotoxic. Rat liver, S9 preparations were used for metabolic activation during the treatments. For each of 10 compounds that differ widely in chemical structure, requirements for metabolic activation and mechanism of action, the concentrations that reduced the surviving fraction and DNA synthesis by 37% and the induced mutant frequency/nmol (IMF/nmol) were determined from dose response data. Aflatoxin B1 (AFB1) gave an IMF/nmol 6 orders of magnitude greater than that produced by ethyl methane sulfonate (EMS). Only hydroxy urea produced an IMF/nmol less (by 1.5 orders of magnitude) than that of EMS. The Do and Co of AFB1 were approx 4 orders of magnitude lower than those of EMS. The ratio IMF/Do produced by AFB1 was approx 25-fold and 135-fold higher than those produced by EMS and MMS, respectively. Thus Co, which can be determined in 6 hr, Do, determined in 10 days, and IMF/nmol, determined in 3 wk, should be useful as a three-tier screen for genotoxic chemicals. With this screen a quantitative assessment of the genotoxicity of a chemical can be obtained within 6 hr. (no Refs)

MICROBIAL TESTS FOR MUTAGENICITY

10. STUDIES ON CHEMICAL CARCINOGENS. XXI. QUANTITATIVE STRUCTURE-MUTAGENICITY RELATIONSHIP AMONG SUBSTITUTED STYRENE OXIDES.

Tamura N, Takahashi K, Shirai N, Kawazoe Y
Faculty Pharmaceutical Sciences, Nagoya City Univ., Tanabedori, Mizuho-ku, Nagoya 467, Japan
Chem Pharm Bull (Tokyo); 30(4):1393-1400 1982

The relationships between structure and mutagenicity of styrene and eight substituted styrene oxides were studied using the mutagenicity assay on Salmonella typhimurium TA100. Mutagenicity and cytocidal activity were correlated with molecular characteristics. Multiple regression analysis indicated that mutagenicity could be described by a combination of the reactivity of the epoxide group and the log of the Van der Waals volume of the molecule. Cytocidal activity depended only on the partition parameter of the molecule. (21 Refs)

11. DEVELOPMENT OF A BIOLOGICAL SCREENING METHOD TO DETECT POTENTIAL EXPOSURE OF SYNFUEL PLANT WORKERS TO CARCINOGENIC SUBSTANCES.

Hannan MA, Recio L, Enoch HG, Hill RH
Kentucky Dept. Energy, Lexington, KY
Development of a Biological Screening Method to Detect Potential Exposure of Synfuel Plant Workers to Carcinogenic Substances. Available from National Technical Information Service, Springfield, VA, as PB82-192709:, 84 pp., 1981.

The purpose of this project was to determine the feasibility of using the Ames assay as a biological monitoring tool to evaluate exposure to mutagens/carcinogens, which may be possibly generated by a synfuel plant. Phase I of this project consisted of analyzing urine samples of cigarette smokers and non-smokers for mutagenicity in order to establish that this assay can reproducibly detect mutagens present in smokers' urine, as well as to distinguish smoking-related mutagenic urine samples from work-related ones. This was necessary to develop a standardized protocol for urine screening. Phase II consisted of an extension of Phase I to examine mutagen activity as cake-oven workers, exposed to known carcinogens and known to have increased cancer risks. Phase II consisted of an analysis of mutagenic activity in urine samples from volunteer workers at the H-coal pilot plant at Catlettsburg, KY. (Author abstract)

TESTS FOR DNA DAMAGE AND REPAIR

12. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.

Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 98(3):287-318 1982

Repair replication (RR) assayed in isopycnic gradients, RR measured by benzoylated naphthoylated diethylaminoethyl (BND) cellulose, RR assayed by bromodeoxyuridine (BUdR) photolysis, alkaline elution assays, repair of single-strand breaks measured in alkaline sucrose gradients, and loss of adducts from DNA are reviewed. BND cellulose chromatography has not been widely adopted for measurement of RR, despite its relative ease and the fact that multiple samples can be processed simultaneously. The BUdR photolysis method is better suited for screening than most of the other DNA repair assays; it can be well controlled using internal standards, and, if standard repair intervals are used, produces data suitable for precise quantitative comparisons. Alkaline elution appears to be useful for identification of DNA-damaging agents if appropriate quantification is performed; it is sensitive, easy to perform and analyze, applicable both in vivo and in vitro studies, and could be used for simultaneous processing of multiple samples. The alkaline sucrose gradient technique for determining DNA repair appears to have limited usefulness for hazard evaluation. The chemicals tested in the various DNA repair assays are listed in the summary table with chemical classifications, and, where available, carcinogenicity assessments. Most of the chemicals used were known inducers of DNA damage and repair, and known mutagens and carcinogens. Of the 49 compounds listed, 23 are alkylating agents, and an additional 11 are polycyclic aromatic hydrocarbons. On theoretical grounds, evidence of DNA repair is a poor indicator of genetic risk. Thus, risk assessment based on repair data must be highly speculative. (130 Refs)

13. CHEMICAL QUANTIFICATION OF UNSCHEDULED DNA SYNTHESIS IN CULTURED HEPATOCYTES AS AN ASSAY FOR THE RAPID SCREENING OF POTENTIAL CHEMICAL CARCINOGENS.

Althaus FR, Lawrence SD, Sattler GL, Longfellow DG, Pitot HC
(c/o Pitot) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 42(8):3010-3015 1982

Technical modifications of the quantitative determination of unscheduled DNA synthesis in cultured hepatocytes are described which allow for the rapid identification of potentially carcinogenic chemicals on a large-scale screening basis. The test is based on the biochemical quantification of [methyl3H] thymidine incorporation into DNA in the presence of hydroxyurea following isolation of nuclei from hepatocytes treated with the agent under study. This procedure ('nuclei procedure') eliminates most of the background radioactivity which otherwise obscures the stimulation of DNA repair synthesis by agents that induce a relatively weak response. By combining the nuclei procedure with a double-labeling technique, test results can be obtained within a few hr after exposure of hepatocytes to the test agents. A test series involving 41 agents confirmed the reliability of the nuclei procedure for the assay of DNA repair synthesis. In addition, chemicals which had yielded conflicting results previously in the autoradiographic hepatocyte DNA repair test, such as 4-acetylaminofluorene, or which had passed unrecognized in the previous in vitro tests, such as the potent liver carcinogen methapyrilene hydrochloride, scored clearly positive in our test protocol. (Author abstract) (27 Refs)

14. BIOPSY MEASUREMENT OF DNA DAMAGE AND REPAIR IN VIVO: SINGLE-STRAND BREAKS, ALKALI-LABILE BONDS, AND ENDONUCLEASE-SENSITIVE SITES.

Brash DE, Hart RW
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Radiat Res; 91(1):169-180 1982

Measurement of DNA single-strand breaks plus alkali labile bonds by alkaline sucrose density gradient centrifugation was adapted to in vivo biopsy samples by refinement of a sensitive fluorescence assay to detect nanogram quantities of nonradiolabeled single-stranded DNA in high-salt alkaline sucrose. The DNA concentration required is low enough to avoid artifactually rapid sedimentation of aggregated single strands and DNA-membrane complexes and to enable analysis of 8 ul biopsy samples. The fluorescent reagent is 3,5-diaminobenzoic acid-2HCl (DABA). Female Sprague-Dawley rats were subjected to x-irradiation and liver biopsies were analyzed by the new method; UV-irradiated rat liver nuclei were also studied after exposure to increasing concentrations of endonuclease. DABA reacted equally with single- and double-stranded DNA, and thus is not preferential for rapidly renaturing reiterated sequences. The nuclei isolation procedure liberated nearly all nuclei, and the squash procedure did not introduce strand breakage. The present method is suitable for smaller samples and less invasive techniques, such as fine-needle biopsy. It eliminates the problems of aggregated sedimentation and DNA damage by incorporated radiolabel, making it suitable for monitoring the role of DNA alterations of pathogenic processes in vivo. (52 Refs)

15. EXTENT OF EXCISION REPAIR BEFORE DNA SYNTHESIS DETERMINES THE MUTAGENIC BUT NOT THE LETHAL EFFECT OF UV RADIATION.

Konze-Thomas B, Hazard RM, Maher VM, McCormick JJ
(c/o Maher) Carcinogenesis Lab.-Fee Hall, Michigan State Univ., East Lansing, MI, 48824
Mutat Res; 94(2):421-434 1982

Predictions that excision repair-proficient cells treated just prior to S will be significantly more sensitive to the cytotoxic and/or mutagenic effect than will be cells exposed many hr prior to S and that cells which are incapable of excision repair will show no difference in sensitivity were tested. Results obtained with UV radiation as the DNA-damaging agent indicated that semi-conservative DNA synthesis is indeed, the 'critical cellular event' responsible for mutation induction. However, the cytotoxic effect of the agent was not significantly increased in normal fibroblasts treated just prior to S phase, even though the cells' excision repair capacity was critical in determining the survival level ultimately attained. (26 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

16. MUTAGEN FORMATION AFTER THE ADDITION OF NITRITE TO NORMAL HUMAN GASTRIC JUICE.

Gatehouse DG, Tweats DJ
Genetic Toxicology Section, Histopathology Dept., Glaxo Group Res. Ltd., Park St., Ware, Hertfordshire, England
Carcinogenesis; 3(5):597-598 1982

The World Health Organization (WHO) has recently recommended the use of a simple in vitro test (Nitrosation Assay Procedure, NAP) to allow the ranking of orally administered drugs. It was suggested that the ranking of drugs should be carried out on a reactivity scale, according to their ability to nitrosate in the presence of high concentrations of nitrite at low pH (3-4). The present study was undertaken to investigate the effect of adding the concentration of nitrite recommended for the NAP test (40 mM) to normal fasting human gastric juice. The data clearly demonstrate that such treatment results in the formation of derivatives with specific mutagenic activity for the bacterium Salmonella typhimurium TA1537. This strain was recommended for use in the NAP Test. Although the NAP test may be valid for its original purpose, in the absence of more physiologically relevant data it is invalid for use as a final arbiter in risk-benefit assessments. The possible formation of mutagenic species as a result of the nitrosation of natural gastric secretions should be considered when any risk-benefit assessment is made. (Author abstract) (18 Refs)

17. ACTIVATION OF TRP-P-1 AND TRP-P-2 IN VITRO AND IN VIVO.

Dolara P, Caderni G, Benetti D
Inst. Pharmacology and Toxicology, Univ. Florence, Florence, Italy
Nutr Cancer; 3(3):168-171 1982

Isolated perfused livers were not able to activate the promutagens Trp-P-1 and Trp-P-2 to their genotoxic metabolites. On the contrary, inherently active mutagenic compounds were detected in the bile of living rats to which Trp-P-1 and Trp-P-2 had been administered intravenously. The excretion of active mutagens through the bile may explain the tumorigenic effect that these compounds exert on the liver during chronic feeding experiments. (Author abstract) (8 Refs)

18. STUDIES ON THE METABOLIC ACTIVATION OF BENZIDINE BY ISOLATED RAT HEPATOCYTES.

Brouns RM, Bos RP, Van Doorn R, Henderson PT
Inst. Pharmacology and Toxicology, Univ. Nijmegen, Nijmegen, The Netherlands
Toxicology; 23(2/3):235-247 1982

Isolated parenchymal liver cells of adult male Wistar rats were exposed to benzidine and the mutagenic activity of the resulting metabolite in the Ames Salmonella typhimurium assay was determined. Induction of DNA repair in the liver cells themselves was also studied. Intact rat liver cells metabolized the benzidine to more mutagenic derivatives than did the 9,000-g supernatant from the hepatocytes. Harmine (an inhibitor of N-acetyltransferase), markedly reduced the mutagenicity of derivatives produced, whereas, salicylamide (an inhibitor of sulfotransferase), had no influence. A time-dependent enhancement of mutagenicity in the Ames assay was observed when benzidine was pre-incubated with intact rat liver cells before being exposed to the 9,000 g supernatant; revertant colonies attained levels 4x those observed when only untreated supernatant was used. Exposure of liver cells to benzidine resulted in a concentration-dependent increase in 3H-thymidine incorporation up to approx 10(-5) M benzidine. Decreasing the N-acetylation and sulfation capacity of the liver cells with harmine and salicylamide, respectively, decreased the incorporation of 3H-thymidine to the level observed in the absence of benzidine, suggesting that both reactions are involved in the generation of reactive metabolites in the liver cell. Evidence was found for an N-acylated metabolite that, when activated by the 9,000 g supernatant, was considerably more mutagenic than benzidine itself. A tentative reaction scheme is presented. (22 Refs)

19. THE COOPERATIVE ROLE OF BACTERIAL AND MAMMALIAN ENZYMES IN MUTAGENIC ACTIVATION OF NITRO-PAH COMPOUNDS (MEETING ABSTRACT).

Pederson TC, Siak JS
Biomedical Science Department, GM Research Laboratories, Warren, MI, 48090
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

The NADPH-Dependent enzyme activity in rat liver microsomes can significantly increase the mutagenicity of several nitro-substituted PAH (polynuclear aromatic hydrocarbon) compounds in the Salmonella/S9 mutation assay under appropriated assay conditions. The enhanced mutagenicity of 2-nitrofluorene (2NF), 1-nitropyrene (1NP), 6-nitrochrysene (6NC) and 6-nitrobenzo(a)-pyrene (6NBaP) in the presence of S9 enzymes can be detected using strain TA98 or the niridazole-resistant strain TA98NR. The S9-dependent activation of 6NBaP, like that of BaP, can also be observed using the dinitropyrene-resistant strains TA98/1,8-DNP6 and TA98NR/1,8-DNP2. In contrast, there is little or no detectable activation of 2NF, 1NP or 6NC by S9 enzymes in assays employing the dinitropyrene-resistant strains, suggesting that the S9-dependent mutagenicity of these compounds towards TA98 and TA98NR requires bacterial nitroreductase activity for formation of the ultimate mutagenic metabolites. This interpretation is supported by experiments with 1NP which demonstrate that an extractable mutagenic metabolite accumulates during incubation with S9 enzymes. The chromatographic and spectroscopic properties of this metabolite suggest it is a hydroxylated derivative of 1NP. It exhibits a high mutagenicity with TA98 and TA98NR but is markedly less active towards the dinitropyrene-resistant strains. There is no evidence to suggest that the S9-dependent activation of 6NBaP involves bacterial nitroreductase activity. This compound may be activated entirely by S9 enzyme activity to form a reactive product such as an epoxide. Thus, the increased mutagenicity of a nitro-PAH compound in the Salmonella/S9 assay may be either dependent or independent of bacterial nitroreductase activities. (no Refs)

20. HUMAN BREAST CELL MEDIATED MUTAGENESIS (MEETING ABSTRACT).

Gould MN, Cathers LE, Moore CJ
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:317 1982

We compared the ability of human and rat mammary cells to activate chemical carcinogens. Both human and rat mammary glands were enzymatically dispersed and separated into stromal and parenchymal enriched populations. The natures of these fractions were confirmed by light and electron microscopy. Stromal and parenchymal populations from both species were cultured at varying cell densities. After the mammary cells attached, they were irradiated with 5000 rad and then cultured with V-79 cells. The co-cultures were exposed to DMBA (dimethylbenzanthracene) (1 ug/ml) for 45 hours. The cultures were then washed and the V-79 cells were removed and assayed for the induction of mutations at the HGPRT locus. Each of the four cell populations activated DMBA. The number of induced mutants was related to the density of mammary cells plated within each species. We found that both the parenchymal and stromal cells could activate DMBA to an equivalent extent, as measured by induced mutation. However, at optimal cell densities the rat cells induced about four times the number of mutations as did the human cells. In addition, we compared these cells for the ability to convert polycyclic hydrocarbons to water-soluble metabolites. Both human and rat stromal cells were more efficient at converting DMBA and BP to water-soluble products than were their respective epithelial cell populations. Rat stromal and parenchymal cells converted BP to water-soluble derivatives more efficiently than their human counterparts. (no Refs)

21. RELATIONSHIP OF POLYCYCLIC HYDROCARBON (PH) METABOLISM IN RAT MAMMARY CELLS TO TUMOR SUSCEPTIBILITY IN VIVO (MEETING ABSTRACT).

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Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:318 1982

Since tumor induction rates by PHs vary widely among rat strains, we have confirmed the high susceptibility of Sprague-Dawley (SD) rats to mammary tumorigenesis by 7,12-dimethylbenz(a)anthracene (DMBA) compared to the Long-Evans (LE) strain. We have also found a similar difference between two inbred rat strains, Wistar-Furth (W/Fu) and F344, respectively. Using cultured mammary cells, divided into epithelial or stromal enriched populations, from these 4 strains, we examined DMBA and benzo(a)pyrene (B(a)P) metabolism in relation to in vivo differences in tumor induction rates. B(a)P was converted to water-soluble metabolites at significantly higher rates than DMBA, with a constant ratio of metabolism of the two PHs, in all cell systems tested. The stromal cell populations, which are less susceptible to carcinogenesis in vivo, converted B(a)P and DMBA to water-soluble metabolites 2-4 times faster than the epithelial cell cultures. In contrast, cells from the high susceptibility strains, SD and W/Fu, showed higher levels of water-soluble metabolite production than the less susceptible strains. High-pressure liquid chromatographic analysis of ethyl acetate-extractable B(a)P metabolites formed in both mammary cell populations from all 4 strains revealed predominantly 9,10-and some 7,8-dihydrodiol formation, but no major differences by cell type or rat strain. We have measured activation of DMBA and B(a)P to mutagenic metabolites by mammary cells from SD and LE rats, and found similar rates in both strains. (no Refs)

22. METABOLIC ACTIVATION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES BY RAT ZYMBAL'S GLAND (MEETING ABSTRACT).

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National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:321 1982

A target tissue for many carcinogenic aromatic amines in the rat is the Zymbal's gland. Because of recent findings that the N-propionyl derivative of N-hydroxy-2-aminofluorene (NP) was a potent carcinogen in this tissue, we have compared the in vitro metabolism of NP to the less carcinogenic N-acetyl (NA) and N-formyl (NF) derivatives. The Zymbal's glands from S/D rats were removed, homogenized and fractionated by centrifugation into the 9000 x g supernatant (S9), cytosol, and microsomes. N,O-Acyltransferase (AT) (assayed by tRNA:fluorenyl adduct formation) and deacylase (assayed by N-hydroxy-2-aminofluorene formation) activities were determined using these fractions. The cytosol was further fractionated by gel-filtration. AT assays showed activities as follow: for S9, NF greater than NP greater than NA; for cytosol, NF greater than NP greater than NA; and for microsomes, NF much greater than NA greater than NP. Paraoxon inhibited adduct formation catalyzed by the cytosol fractions for NF, and by microsomes for NF, NP, and NA. In contrast, deacylase assays were as follows: S9, NP greater than NA much greater than NF; cytosol, no activity; and microsomes, NP much greater than NA much greater than NF. All deacylase reactions were paraoxon-sensitive. Gel-filtration chromatography of cytosol demonstrated two AT's: an early eluting fraction with high specificity for NF; and a later eluting fraction exhibiting activity for NP. Relative Zymbal's gland AT activity, compared to liver AT activity, is about 0.03 for NA, 0.3 for NP and 1 for NF. Zymbal's gland deacylase activity, compared to liver deacylase activity, is about 2x for NA and about 3x for NP. Deacylation appears to be the major metabolic pathway in Zymbal's gland homogenates for NP and NA. Moreover, deacylase activity corrrelates with the tumor incidence observed in Zymbal's gland (NP greater than NA greater than NF). (no Refs)

23. A CELL-MEDIATED MUTAGENESIS ASSAY FOR DIMETHYLNITROSAMINE IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

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University of Southern California Cancer Center, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:361 1982

The C3H/10T1/2 mouse embryo fibroblast cell line is widely used as a quantitative system to measure oncogenic transformation and mutagenesis. These cells metabolize a number of chemical carcinogens, such as polycyclic aromatic hydrocarbons, to derivatives that produce cytotoxicity, mutagenicity, and cell transformation. However, these cells are incapable of activating some other classes of carcinogens, such as dimethylnitrosamine (DMN). Hence, an activation system has been developed, with emphasis on DMN. We use primary rat liver hepatocytes, prepared by a modification of the procedure of Jones and Huberman, as the activating system for C3H/10T1/2 target cells. The target cells and the hepatocytes are cocultivated for 24 hr at a target cell to hepatocyte ratio of 1:5; after treatment the cells are reseeded, and 24 hr later the selective agent, ouabain (3 mM) is added. Under these conditions DMN causes a dose-related cytotoxicity and mutagenesis; the relative plating efficiencies of the C3H/10T1/2 cells at 1 mM, 100 uM, and 10 uM DMN were 49%, 48%, and 92% respectively. The mutation frequencies X 10(6) were 116, 70.5, and 36.9. The control value was 2.6. In comparative studies of this cell-mediated activation system with S-9 liver homogenate induced with Aroclor 1254 and with an irradiated epithelial cell line (ML 21) derived from regenerating C3H mouse liver, significant activation of DMN was only achieved with the primary hepatocytes. (1 Ref)

24. RETINOIDS AS INHIBITORS OF ORTHO-AMINOAZOTOLUENE-INDUCED MUTAGENESIS IN THE SALMONELLA/LIVER MICROSOME TEST.

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Mutat Res; 104(4/5):225-231 1982

To determine the optimal conditions for ortho-aminoazotoluene (OAAT) mutagenicity in the Salmonella/liver microsome assay, three doses of OAAT (2, 4, and 8 ug/plate) were tested in the presence of various amounts of rat-liver homogenate (10, 20, 30, 50, 70, and 90 ul/plate). Thirty ul S9/plate yielded maximal mutagenicity, whereas the addition of larger or smaller amounts of rat-liver homogenate decreased mutagenic activity. OAAT was tested in the presence of various amounts of retinol, retinol acetate, and retinol palmitate ranging from 0-525 nanomoles/plate. Under optimal conditions (30 ul S9/plate), retinol inhibited the OAAT-induced mutagenicity almost completely. (10 Refs)

25. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

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Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct- and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate, and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

26. AN EVALUATION OF THE HOST-MEDIATED ASSAY AND BODY FLUID ANALYSIS. A REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.

Legator MS, Bueding E, Batzinger R, Connor TH, Eisenstadt E, Farrow MG, Ficsor G, Hsie A, Seed J, Stafford RS
Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
Mutat Res; 98(3):319-374 1982

Host-mediated assay (HMA) and body fluid analysis (BFA) are reviewed. The HMA is capable of detecting diverse groups of chemical mutagens by making use of a wide range of indicator systems. Chemicals requiring metabolic activation (including non-hepatic activation) are rendered biologically active mutagens by the host animal. Furthermore, these active metabolites of the administered chemicals are able to come in contact with the indicator, which is usually located in the peritoneal cavity. The immunological system of the host may alter the integrity of the indicators so that the mutagenic response is altered. Of 208 chemicals that were evaluated in the HMA, 133 were mutagenic with one or more indicators. BFA in animals can provide useful information on the in vivo formation of mutagenic substances and can be used to identify exposure to mutagens in man. The limit of BFA, in terms of both method and predictive value, have not been assessed. The value of pretreating test fluids with deconjugated enzymes is uncertain. While a positive result obtained after enzymatic hydrolysis of conjugates indicates that mutagenic species are being generated in vivo, the presence of conjugates is also indicative of the capability of in vivo defense mechanisms to detoxify these agents, although a few exceptions may exist. Thus, false-positive responses could be obtained. Results of BFA could be more indicative of genetic risk than results from strictly in vitro tests. (193 Refs)

27. USE OF AMES TEST TO DETERMINE PROCARCINOGEN ACTIVATION POTENTIAL OF A CELL LINE USED FOR MUTAGEN/CARCINOGEN TESTING (MEETING ABSTRACT).

Swierenga SH, Matula T
Drug Toxicology Division, Health and Welfare Canada, Ottawa K1A 0L2, Canada
In Vitro; 18(3,part2):288 1982

The successful use of mammalian cultured cells in mutagen/carcinogen testing depends on the presence (endogenous or exogenous) of adequate activation systems for procarcinogen metabolism. To determine whether an established cell line derived from rat liver (T51B) has retained the ability to activate a variety of procarcinogens after numerous passages in vitro, these compounds were tested with standard Ames Test, by substituting the tissue culture cells for the usual S-9 microsomes. Tester strains TA100, TA1538 and TA98 were preincubated with carcinogen, NADPH2 generating system, and aliquots of T51B cells for 1 h before plating for bacterial mutation. Quantitation of mutants formed after 48 h incubation showed that the liver cells had only a very weak capability of mediating bacterial mutation with benzo(a)pyrene, 3-methylcholanthrene, aflatoxin B2, and 2-acetylaminofluorene; but were potent activators of the aromatic amine 2-aminoanthracine, eliciting a dose reponse and a mutagenic effect comparable to standard S-9. Thus different cell lines may be 'specialists' for the activation of specific types of compounds and the use of exogenous activation systems is recommended. (no Refs)

28. GENOTOXICITY AND METABOLISM OF CHOLESTEROL EPOXIDE IN V79 CHINESE HAMSTER CELLS (MEETING ABSTRACT).

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Institute for Toxicology and the Cancer Center, University of Southern California, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:371 1982

Cholesterol oxidation results in a number of products that are potentially genotoxic. Attention has been given to cholesterol-5alpha, 6alpha-epoxide (CE), which can be formed by mixed function oxidation of cholesterol as well as by autoxidation. However, recent evidence indicates that the hydration product of CE, cholestan-3beta, 5alpha, 6alpha-triol (CT), may be more toxic than CE. Conflicting literature on the genotoxicity of CE led to an examination of the properties of this steroid using a three-tiered screen for genotoxicity. Chinese Hamster cell cultures were used to examine the effects of pure CE and CT on DNA synthesis (FI, fractional incorporation of [3H],-dThd) cytotoxicity (S, surviving fraction of single cells) and mutation frequency (IMF, induced 8-azaguanine-resistant mutant frequency). Dose-response studies showed that CE caused a progressive decline in FI and S up to 75 ug/ml, beyond which precipitation occurred. IMF showed a biphasic response with increasing concentration. These effects were linearly time dependent. A treatment with 25 ug/ml CE for 24 hr produced a 50% decrease in FI and S and an IMF of 24 +/-5 mutants/10(5) survivors (3 experiments). Similar effects were found with CT at lower concentrations (10 ug/ml) and observed as early as 2 hr after treatment. The metabolic conversion of CE to CT may explain these observations, and studies on the metabolism and genotoxicity of CT will be presented. (no Refs)

COMPARATIVE TEST RESULTS

29. MUTAGENICITY TESTS WITH DOMPERIDONE IN VITRO AND IN VIVO.

Vanparys P, Fabry L, Leonard A, Marsboom R
Lab. Toxicology, Veterinary Dept., Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium
Toxicol Lett; 12(2/3):215-222 1982

Induction of chromosome damage by domperidone was investigated in vivo by a micronucleus test on Albino Swiss mice and in a dominant lethal test on both male and female mice. In vitro chromosome damage was assessed in short-term cultures of human lymphocytes. No chromosome aberrations were observed in mammalian cells in vivo and in vitro, even in the presence of microsome enzymes. (13 Refs)

30. MITOCHONDRIAL AND NUCLEAR MUTAGENICITY OF ELLIPTICINE AND DERIVATIVES IN THE YEAST SACCHAROMYCES CEREVISIAE.

Pinto M, Guerineau M, Paoletti C
INSERM U178, Hopital Broussais, 96 rue Didot, 75674 Paris, Cedex 14, France
Biochem Pharmacol; 31(12):2161-2167 1982

Haploid strains of the yeast Saccharomyces cerevisiae were tested for their sensitivity to ellipticine and nine derivatives; some of them exhibiting antitumor properties. Different mutagenic properties of ellipticines are described. Charged ellipticines, which were ineffective in Ames' bacterial assay, were found to be potent inducers of the mitochondrial rho- mutation: induction proceeded even in the absence of growth. Uncharged ellipticines increased mitochondrial antibiotic resistance mutations, whereas charged derivatives decreased them. Ellipticine derivatives enhanced, reduced, or did not change the reversion frequencies of nuclear auxotrophic markers. The result depended on the strain being tested: no structure-effect relationship existed. As some ellipticine derivatives were mutagenic in Saccharomyces cerevisiae despite being ineffective in Ames' assay, multiple tests should be used to check that chemotherapeutic drugs are devoid of mutagenic properties. (Author abstract) (32 Refs)

31. MAMMALIAN ACTIVATION AND METABOLISM OF 1-NITROPYRENE (MEETING ABSTRACT).

Ball LM, Kohan MJ, Claxton L, Lewtas J
Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, 27711
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

We have used 1-nitropyrene (NP) as a model Nitrated polycyclic organic compound (NPOC), to investigate potential genotoxicity in mammalian systems. NP was generally non-mutagenic in bioassays conducted in Chinese hamster ovary cells, and in the mouse lymphoma L5178Y system. However with the addition of a metabolic activation system consisting of the S-9 fraction from Arochlor-induced rat liver. NP proved to be more mutagenic than benzo(a)pyrene in the latter assay. NP also induced unscheduled DNA synthesis in primary rat hepatocytes. The ability of S-9 to activate NP was confirmed by assay in the Salmonella nitro-reductase-deficient strain TA98FR1, in which NP exhibits minimal 'direct-acting' mutagenicity. S-9 increased the mutagenicity of NP seven-fold,and microsomes derived from the S-9 produced a twenty-fold increase. 1-Aminopyrene and N-acetylaminopyrene, the principal reductive metbolic products of NP, have been identified by HPLC (high performance liqiud chromatography) in incubations of NP with S-9. Other metabolites were tentatively identified as phenols produced by aromatic ring oxidation. Thus some mammalian enzyme systems are indeed capable of carrying out the metabolic reactions associated with genotoxic activity in microbes. The contribution of the oxidative metabolic products to the geno- and cytotoxicity seen in mammalian cells remains to be evaluated more closely. (no Refs)

32. METABOLISM OF 7H-DIBENZO(C,G)CARBAZOLE IN SPRAGUE-DAWLEY RAT LIVER MICROSOMES (MEETING ABSTRACT).

Warshawsky D, Myers BL, Dooley J, Schoeny R, Christian R
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Proc Am Assoc Cancer Res; 23:320 1982

The metabolism and mutagenicity of 7H-dibenzo(c,g)carbazole (DBC) is under investigation in our laboratory. Incubation of DBC with liver microsomes prepared from 3-methylcholanthrene-treated (3MC) rats resulted in the production of nine metabolites separable by HPLC (high pressure liquid chromatography) and characterized by spectroscopic techniques. Further identification of the metabolites and delineation of the metabolic pathways of DBC were accomplished by incubation of DBC and enzyme inhibitors/ activators (styrene oxide, trichloropropene oxide, cyclohexene oxide, glycidol or SKF525A) with rat liver microsomes followed by HPLC. Metabolites 1 and 2 were identified as dihydrodiols while metabolites 3 through 5 were identified as phenols. DBC was found to be mutagenic for a Chinese hamster epithelial line DPI-3, when cocultivated with Syrian hamster embryo (SHE) cells using 6-thioguanine for selection. Results of Salmonella/ microsomal reverse mutation assays were equivocal for DBC. Forward assays to 8-azaguanine resistance using Salmonella strain TM677 showed DBC to be nonmutagenic. When assayed in DPI-3/SHE system metabolites 5, 7, and 8 were mutagenic. In the forward mutation assay the mutagenicity of DBC metabolites was dependent upon the activation system; without S9, metabolite 2 was positive; 3MC S9, no metabolites were positive; Aroclor 1254 S9, 3b was mutagenic. (no Refs)

33. MUTAGENICITY STUDY OF FRIED SAUSAGES IN SALMONELLA, DROSOPHILA AND MAMMALIAN CELLS IN VITRO AND IN VIVO.

Gocke E, Eckhardt K, King MT, Wild D
Inst. Molecular Biology, Univ. Aarhus, 8000 Aarhus, Denmark
Mutat Res; 101(4):293-304 1982

An extract of pan-fried sausage was tested in an array of systems, including the Salmonella/microsome test, the Drosophila sex-linked recessive lethal test, tests for induction of sister-chromatid exchange and point mutations in V79 Chinese hamster cells, the micronucleus test, the intrasanguine host-mediated assay, and the mammalian spot test. Results suggest that mice and possibly mammals in general are less sensitive than Salmonella towards the mutagens produced during frying of meat. The mutagenic risk of traces of promutagens in fried meat is orders of magnitude lower than would be estimated using the Ames plate test as a guideline. However, genetic activity of the mutagenic principles of fried meat in mammalian systems cannot be excluded. (29 Refs)

34. MUTAGENICITY TESTS AND IN VITRO TRANSFORMATION ASSAYS ON TRIETHANOLAMINE.

Inoue K, Sunakawa T, Okamoto K, Tanaka Y
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Mutat Res; 101(4):303-313 1982

The mutagenicity and cell-transforming activities of triethanolamine were examined by measuring induction of DNA damage in Bacillus subtilis, mutagenicity in Salmonella typhimurium and Escherichia coli, production of chromosomal aberrations in Chinese hamster cells, and transformation of hamster embryo cells. Diethanolamine and monoethanolamine were also examined for induction of transformation. The results suggest that triethanolamine may not produce genotoxic effects by reaction with DNA and consequent induction of changes in DNA structure and function. The increased incidence of tumors induced in female mice by triethanolamine may be a secondary or indirect result of some specific cytotoxic effect. (20 Refs)

35. A MARINE HOST-MEDIATED ASSAY FOR THE DETECTION OF MUTAGENIC COMPOUNDS IN POLLUTED SEA WATERS.

Frezza D, Pegoraro B, Presciuttini S
Istituto di Biologia del Mare, C.N.R., Venezia, Italy
Mutat Res; 104(4/5):215-223 1982

A host-mediated assay (HMA) for the detection of mutagenic compounds was developed using mussels grown in both clean and polluted areas and clean mussels transferred for a period of time into polluted areas. Two strains of yeast were used as genetic indicator microorganisms; results were compared with those obtained by treating the same yeast strains, TA98 and TA100 of Salmonella typhimurium, with the corresponding mussel extracts. The direct mutagenic activity of mussel extract on yeast and bacteria was dose-dependent; however, the induced mutagenic frequency never exceeded a value corresponding to approx 5x the spontaneous frequency. (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

36. MUTAGENICITY AND K-REGION REACTIVITY OF MONOMETHYL DERIVATIVES OF BENZ(A)ANTHRACENE IN A SELF-CONSISTENT-FIELD MOLECULAR ORBITAL THEORY.

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Dept. Physics, Univ. New Delhi, Delhi 110007, India
Biochem Biophys Res Commun; 106(3):836-841 1982

A self-consistent-field (SCF) molecular orbital (MO) theory was used to examine how the mutagenicity of monomethyl derivatives of benz(a)anthracene (MBA) is related to the corresponding reactivity of the K-region where the addition reactions are likely to occur. The total pi-electron density in the K-region was used as an appropriate index measuring the reactivity of the K-region towards epoxidation. The calculated SCF values of the difference in total pi-electron density in the K-region (deltaQK) were compared with the mutagenicity as demonstrated by the Ames test for the MBA. Huckel molecular orbital (HMO) values are also given. The K-region reactivity as represented by the SCF values of deltaQK for the MBA correlated well with the observed mutagenicity. The only exceptions were the high mutagenicities of 4-MBA and the K-region derivatives, 5-MBA and 6-MBA. Except for the aforementioned compounds, the free valence was always max at the K-region, suggesting that for the exceptions, the K-region reactivity may not be the only controlling factor. The correlation between K-region reactivity and mutagenicity almost disappeared when the HMO values of deltaQK were used instead of the SCF values. The K-region theory, however, cannot account for most of the qualitative data on the corresponding carcinogenic potencies of the MBA. (16 Refs)

37. GUIDELINES FOR STUDIES OF HUMAN POPULATIONS EXPOSED TO MUTAGENIC AND REPRODUCTIVE HAZARDS. PROCEEDINGS OF A CONFERENCE HELD IN WASHINGTON, D. C., 26-27 JANUARY, 1981.

Bloom AD
Dept. Pediatrics and Human Genetics and Development, Coll. Physicians and Surgeons, Columbia Univ., New York, NY
Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards, Proceedings of a Conference held in Washington, D. C., 26-27 January, 1981. White Plains, NY, March of Dimes Birth Defects Foundation. 163 pp., 1981.

Panels were established to study cytogenetic effects of genotoxic chemicals on human populations, reproductive effects of genotoxic chemicals, and testing for mutagens in human populations. Discussion of cytogenetic study guidelines included presentation of background information, methods for study of induced chromosomal aberrations, analysis and classification of chromosomal structural changes, analysis of data on structural aberrations, methods and procedures for analysis of sister chromatid exchange (SCE) in human lymphocytes, and significance of aberrations and SCE. Reproductive study guidelines are considered in relation to indices of reproductive failure, statistical issues, guidelines for Level I activities (accessible sources), decision making (moving from Level I to Level II), long-term follow-up studies (Level III), and data on selected end points. Topics discussed with regard to detection of gene mutation and DNA damage in the human population included the following: background information, the need for genetic monitoring, criteria for defining a human population at risk, methods potentially useful for evaluating human populations exposed to mutagenic hazards, and current status of the use of mutation assays to evaluate human populations. Implementation of the guidelines must consider cost of inadequate evaluations of potential mutagens and teratogens, coordination of the three sets of guidelines, and statistical concerns. (384 Refs)

38. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.

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J Chronic Dis; 35(7):581-600 1982

Techniques with potential usefulness in molecular cancer epidemiology are reviewed, with special emphasis placed upon a highly sensitive assay that detects covalent binding of the polycyclic aromatic hydrocarbon benzo(a)pyrene to human DNA. Benzo(a)pyrene has assumed considerable importance among chemical carcinogens because it has proven carcinogenic potency in a variety of species and tissues, it is ubiquitous in the environment, and there is extensive information regarding its metabolism and mode of action. Laboratory methods applicable to molecular cancer epidemiology include techniques to assess specific host factors that may influence susceptibility to carcinogens; assays that detect carcinogens in human tissues, cells, or fluids; assays at the cellular level of biologically effective doses of carcinogens; and methods to measure early biologic and biochemical responses to carcinogenic agents. Inherited and acquired host factors that may influence human susceptibility to carcinogens, methods for detecting and quantitating chemical carcinogens in human tissues or body fluids, markers for assessing the biologically effective dose of carcinogens in humans, potential markers for early biological and biochemical response to carcinogens in humans, and the immunoassay of benzo(a)pyrene-DNA adducts as an example of a promising marker in molecular cancer epidemiology are among topics discussed. (229 Refs)

39. OECD GUIDELINES FOR TESTING OF CHEMICALS.

Organisation for Economic Co-operation and Development
Organisation for Economic Co-operation and Development, 2, rue Andre Pascal, 75775 Paris Cedex 16, France
OECD Guidelines for Testing of Chemicals (Paris: Organisation for Economic Co-operation and Development):; 64pp 1981

Official Organisation for Economic Co-operation and Development (OECD) guidelines for testing of chemicals as adopted by the OECD Council are presented. The guidelines contain generally formulated procedures for the laboratory testing of a property or effect deemed important for the evaluation of health and environmental hazards of a chemical. Physical-chemical properties, effects on biotic systems other than man, degradation, accumulation, and long- and short-term health effects are covered. Short-term toxicology is discussed including acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, acute dermal irradiation/corrosion, skin sensitization, repeated dose oral toxicity (rodent: 14/28 days), subchronic oral toxicity (rodent: 90 days; non-rodent: 90 days), repeated dose dermal toxicity (21/28 days), subchronic dermal toxicity (90 days), repeated dose inhalation toxicity (14/28 days), subchronic inhalation toxicity (90 days), and teratogenicity. Long-term toxicology includes carcinogenicity studies, chronic toxicity studies, and combined chronic toxicity/carcinogenicity studies. An appendix includes the decision of the OECD Council concerning mutual acceptance of data in the assessment of chemicals, including the OECD principles of good laboratory practice. (36 Refs)

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1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.

Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
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2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.

Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
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RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.

National Radiological Protection Board
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The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

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Leber Magen Darm; 12(3):95-107 1982
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Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.

Magnus K
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(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
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Vena JE
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Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
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Lipetz PD, Galsky AG, Stephens RE
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Adv Cancer Res; 36:165-210 1982

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Fedorov NA
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Carcinogenesis 7: 664 pp., 1982.

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Graf T, Stehelin D
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Biochim Biophys Acta; 651(4):245-271 1982

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Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

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21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.

Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
J Chronic Dis; 35(7):581-600 1982

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(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 98(3):377-387 1982

23. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.

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Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
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Legator MS, Bueding E, Batzinger R, Connor TH, Eisenstadt E, Farrow MG, Ficsor G, Hsie A, Seed J, Stafford RS
Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
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TESTS FOR CELL TRANSFORMATION

1. IN VITRO TRANSFORMATIONS OF HUMAN AMNIOTIC CELLS IN THE PRESENCE OF FECALASE. THE DEVELOPMENT OF DETECTION TESTS FOR THE ONCOGENIC POTENTIAL OF CHEMICAL SUBSTANCES IN THE ENVIRONMENT.

Aranda M, Dorange J, Turc C, Flori E, Zahnd J

Laboratoire de Cytogenetique, Faculte de Medecin, 7, boulevard Jeanne d'Arc, 21003 Dijon, France

C R Soc Biol (Paris); 176(1):39-44 1982

Fecalase (FCL) was used to study the carcinogenic activity of 8-hydroxyquinoline-beta-D-glycopyranoside (8 HQG). Without FCL, 8HQG, did not induce any changes in cells colonies. In the presence of FCL, there was obvious induction of transformed cells. Results indicated the value of human FCL in studying the carcinogenicity of food glycosides. (11 Refs) (In FRE)

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2. CHEMICAL COCARCINOGENESIS IN A SUBCLONE OF BALB/3T3 CELLS USING CATECHOL AS COCARCINOGEN (MEETING ABSTRACT).

Atchison M, Chu CS, Van Duuren BL
New York University Medical Center, New York, NY, 10016
1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

This study was carried out to determine cocarcinogenesis in vitro using a subclone of a Balb/3T3 cell line. The cells were grown in minimum essential medium (MEM). Dose response, cytotoxicity and transformation studies were performed using an indirect-acting carcinogen, benzo(a)pyrene (BaP), a direct-acting alkylating carcinogen, beta-propiolactone (BPL), and the mouse skin cocarcinogen catechol. The rate of transformation was notably higher in groups treated with BaP and catechol or BPL and catechol than in groups treated with either BaP or BPL alone. Catechol alone did not induce any transformation. All the cells isolated from the transformed foci showed characteristics of malignant transformation such as anchorage-independent growth in soft agar. Thus, chemical cocarcinogenesis was accomplished in vitro similar to the in vivo mouse skin experiments. The results in this report clearly demonstrate the cocarcinogenic activity of catechol on BaP as well as BPL-induced transformation in vitro. This system can now be used with the dual purpose of studying mechanism of action of cocarcinogens in vitro, and as a short-term in vitro bioassay for other potential environmental cocarcinogenic agents. (no Refs)

IN VIVO TESTS FOR MUTAGENICITY

3. MUTAGEN ASSAY WITH ARABIDOPSIS: A REPORT OF THE U. S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.

Redei GP
Univ. Missouri, Columbia, MO, 65211
Mutat Res; 99(2):243-255 1982

Use of the small crucifer Arabidopsis for short-term assays of mutagenesis is reviewed. Such assays can detect forward mutations of a large number of loci in less time and with less expense than with other higher organisms. The Arabidopsis assay is apparently suitable for in situ tests of environmental pollutants, particularly soil- and water-borne pollutants. Future efforts towards better calibration and standardization, establishment of special genetic stocks, and development of procedures are recommended. (47 Refs)

4. THE PERSISTENCE OF MICRONUCLEI IN PERIPHERAL BLOOD ERYTHROCYTES: DETECTION OF CHRONIC CHROMOSOME BREAKAGE IN MICE.

Schlegel R, MacGregor JT
United States Dept. Agriculture, Western Regional Res. Center, 800 Buchanan St., Berkeley, CA, 94710
Mutat Res; 104(6):367-369 1982

Following eight ip injections of 0.2 mg/kg triethylene-melamine (TEM), bone marrow RBC of male Swiss-Webster mice exhibited a steady increase in the incidence of micronuclei. This elevated level did not return to normal values until approx 30 days after TEM was discontinued. It was concluded that micronucleated RBC induced by a bone-marrow clastogen accumulate in the peripheral blood of mice and there is very little or no selective removal of these aberrant cells from circulation. Application of this method for assessment of in vivo chromosome breakage in chronic or subchronic toxicity studies is suggested. (7 Refs)

5. EFFECT OF COCULTIVATION ON THE LEVELS OF SPONTANEOUS AND INDUCED SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER CELLS.

Rainaldi G, Luccini F, Mariani T
Instituto di Mutagenesi e Differenziamento C.N.R., Via Svezia, 10, 56100-Pisa, Italy
J Cell Physiol; 112(2):281-283 1982

Levels of spontaneous and induced sister chromatid exchanges (SCE) were investigated in Chinese hamster cells (line V79/AP4) cultivated in the presence or absence of human cells (C5R0 normal human fibroblasts or xeroderma pigmentosum cell line XP25R0 fibroblasts). V79/AP4 cells were grown exponentially then exposed to UV light or ethylmethane sulfonate (EMS). SCE were determined in homogeneous cell populations (hamster:hamster) and heterogeneous cell populations (hamster:human). Cocultivation of hamster cells with human cells resulted in a reduction of the spontaneous level of SCE and in the level of SCE induced by UV light and EMS. When XP cells were used as a probe instead of normal human fibroblasts, it was shown that XP cells were equally effective in lowering the SCE of Chinese hamster cells damaged either by UV or EMS. The reduction appeared to depend strongly on cell density: culturing the same total amount of cells on larger dishes resulted in a disappearance of the reduction effect. Replacement of human fibroblasts with hamster cells did not affect the influence of cell density on SCE reduction; however, when damaged hamster cells were used, the level of SCE was not lowered. Use of cocultivation is suggested for investigating SCE formation processes. (19 Refs)

CELL CULTURE TESTS FOR MUTAGENICITY

6. QUALITY CONTROL CRITERIA FOR THE EVALUATION OF DATA IN THE MOUSE LYMPHOMA 5178Y FORWARD MUTATION ASSAY AT THE TK LOCUS (MEETING ABSTRACT).

Caspary WJ, Lee YJ, Poulton S, Myhr B, Mitchell A, Rudd C
NIH, Bethesda, MD
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Quality control criteria, designed to reject experiments that do not meet minimum quality standards, were defined during an evaluation of the Mouse Lymphoma System as a mutagenicity assay. These criteria are based on an analysis of over 450 experiments from two laboratories. Experiments that meet these criteria may be rejected upon further evaluation. To test the utility and flexibility of the assay, they are designed to represent the least rigorous conditions necessary to produce consistent evaluations between and within laboratories. We reject samples when solvent control cloning efficiencies are outside the 50-115% range, when the cloning efficiency of a dose is less than 10% and when the relative total growth is less than 10% and when the relative total growth is less than 1%. We reject sample sets in which the replicate mutant frequencies do not meet certain statistical standards for precision. Experiments are rejected when there are less than two solvent control per experiment and when the average solvent control mutant frequency is outside the 10-150x10(6) range. At least two positive controls should be acceptable with cloning efficiencies between 10 and 115% and a mutant frequency within the historical range. (no Refs)

7. TUMOR MARKERS IN EXPERIMENTAL ANIMALS (MEETING ABSTRACT).

Mazue G

No affiliation given

International Conference on Safety Evaluation and Regulation, of Chemicals, February 24-26, 1982, Boston, Massachusetts Bio-Research Institute; 1982

Classic carcinogenicity studies are both time- and money-consuming; hence the interest of having at our disposal tests for early detection or, at least orientation. Reliable tests based on mutagenesis now exist for the detection of genotoxic carcinogenic agents. There remain the epigenetic carcinogenic agents, such as promoters. Amongst these tests aimed at revealing potential promoting activity, the search for altered foci and early neoplastic liver lesions is widely used and classic histochemical markers are needed, amongst which those which are resistant to iron loading after induced siderosis. This criterion is both easy to implement and reliable. This cellular dedifferentiation is accompanied by a reapparition of gamma GT (gamma glutamyl transferase) in altered adult rat hepatocytes. The activity of gamma GT (E.C. 2.3.2.2) varies alike in liver homogenates and in blood, and is perfectly correlated with the pathological lesions revealed. The dosage of plasmatic gamma GT can thus be used in the early detection of such lesions and allows the evaluation of their intensity and kinetics. (1 Ref)

8. SHORT TERM BIOASSAY FOR THE DETECTION OF ENVIRONMENTAL MUTAGENS USING HIGH RESOLUTION FLOW CYTOMETRY (MEETING ABSTRACT).

Otto FJ

Fraunhofer-Institut fur Toxikologie und Aerosolforschung, D-5948 Schmallenberg, W. Germany

Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

The technique of flow cytometry has been used to develop an assay for the detection of mutagenic effects in cells. Since chromosomal aberrations and dysfunction of the mitotic apparatus cause an unequal division of the DNA in the daughter cells and subsequently produce an increased dispersion of the DNA content in the cell population, the technique of high resolution flow cytometry is capable of measuring the effect of mutagenic agents in cells from cell cultures or somatic tissues. The procedure has been used to study the effects of different model mutagens in mouse bone marrow in vivo. The broadening of the G1 peak was taken as a criterion for the mutagen-induced increased dispersion of the cellular DNA content. It was quantified by calculating the coefficient of variation in the DNA histograms of the bone marrow cells harvested 48 hours after a single injection of the mutagens. The procedure proved to be fast, reproducible, and at least as sensitive as other cytogenetic methods. The assay may have applications in experimental mutation research and mutagenicity testing. (no Refs)

9. INDUCTION OF MUTATION IN HYPERMUTABLE CELLS: A POSSIBLE RAPID ASSAY FOR CANCER PROMOTERS (MEETING ABSTRACT).

Williams JR, Frank JP, D'Arpa P, Kram D

Department of Radiology, The George Washington University School of Medicine and Health Sciences, Washington, DC

1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

Frank and Williams have demonstrated x-rays to induce in cultured cells a cellular state(s) that has as one phenotype and hypersensitivity to mutation when exposed to subsequent chemical and physical agents. This phenomenon was observed mimicking a sequence of treatments, x-rays followed by PUVA (psoralen + UVL, 365 nm), that induces excess cancer (28X) in treated human patients. We hypothesize that hypermutable cells may be one form of intermediate in multistage carcinogenesis. Thus, cancer promoters which act upon the hypermutable state can easily be defined in a simple cultured cell system as those agents inducing excess mutation in cell populations containing hypermutable cells, compared to their action in control populations. We have evaluated, to various degrees, the ability of 7 agents, including agents known to be directly mutagenic, to produce this effect. UVC (254 nm), PUVA, cell proliferation, mitomycin C, TPA (12-O-tetradecanoylphorbol-13-acetate), acetone, psoralen and DMSO (dimethyl sulfoxide) were tested; only psoralen and DMSO failing to induce excess mutation in populations demonstrated to contain hypermutable cells. We have performed detailed dose response curves for UVC and PUVA, and find excess mutations in hypermutable cells only at doses that are appreciably non-toxic for control cells. This seems a characteristic of hypermutability, important to its possible relevance to carcinogenesis; viz, it is essentially a low-dose phenomenon. Thus, in assaying any agent for its potency in the induction of mutation in hypermutable cells, a series of doses must be evaluated both in populations containing hypermutable cells and in control populations. Current efforts in our laboratory are designed to evaluate whether the ability to induce excess mutation in hypermutable cells compared to control cells is a simple and objective criterion for cancer promoters. (no Refs)

MICROBIAL TESTS FOR MUTAGENICITY

10. STUDIES OF THE SENSITIVITY OF THE YEAST S. CEREVISIAE D7 IN DETECTING MUTAGENS (MEETING ABSTRACT).

Arni P, Muller D
CIBA-GEIGY Limited, CH-4002 Basle, Switzerland
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

For the detection of occupational mutagens the sensitivity of a particular test system in regard to the substances to be tested is of major importance. With 16 substances known to be mutagenic in bacteria, the sensitivities of Saccharomyces cerevisiae D7 and several strains of Salmonella typhimurium were compared, using similar incubation systems (with activation where required). 4-nitroquinoline-N-oxide, MNNG (N-methyl-N'-nitro-N-nitrosoguanidine), mitomycin-C, thiotepa, Trenimon and cyclophosphamide displayed clear-cut effects in the yeast system. The effective concentrations were similar in both test organisms used. With high concentrations of 2-aminoanthracene and 2-acetylaminofluorene positive results with S cerevisiae were also found. Acridine orange, 9-aminoacridine, Adriblastin, Daunoblastin, 2-nitrofluorene, benzo(a)pyrene, isopropylmethanesulfonate and beta-naphtylamine were only barely positive or even negative in the yeast system. (no Refs)

CYTOGENETIC TESTS

11. INTERINDIVIDUAL VARIATION OF CYTOGENETIC DAMAGE BY CYTOSTATIC THERAPY: A CONTRIBUTION TO INDIVIDUAL SENSITIVITY AGAINST CHEMICAL MUTAGENS (MEETING ABSTRACT).

Gebhart E, Losing J, Mueller RL, Windolph B
Institut f. Humanagenetik d. Universitat, Bismarckstr. 10, D - 8520 Erlangen, W. Germany
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Chromosome aberrations, sister chromatid exchanges, and proliferation kinetics were analyzed from cultured blood lymphocytes of patients undergoing a well-defined schedule of cytostatic interval therapy with Methyl-CCNU (Semustine), Fluorouracil, and Vincristine. Analyses from 48h and 72h cultures were performed at identical stages of therapy with different patients, ie from individuals exposed to identical doses (as corresponding with the body surface) of identical cytostatics for identical periods. Distinct differences of the cytogenetic response to the therapy were observed between different individuals concerning the studied parameters. A few patients exhibited and outstanding resistance to the chromosome damaging action of the cytostatics throughout the therapy schedule. It is pointed out that the observed interindividual variability apparently is higher than it is in the standard test systems of mutagenicity testing. (no Refs)

12. STANDARDIZATION OF THE SISTER CHROMATID EXCHANGE TECHNIQUE IN HUMAN LYMPHOCYTES FOR MUTAGEN AND CARCINOGEN TESTING.

Kamlesh S
Western Michigan University, Kalamazoo, MI
Diss Abstr Int [B]; 42(10):3948-B 1982

The differential staining of chromosomes with the use of 5-bromo-2'-deoxyuridine (BUdr) is used extensively to study sister chromatid exchange (SCE). The frequency of SCEs increases significantly in the presence of mutagenic and carcinogenic agents. Hence, the BUdR technique (commonly referred to as the SCE technique) has been useful as a diagnostic tool to test for mutagenic and carcinogenic agents. Investigators have used differential staining to obtain a baseline incidence of SCEs in human lymphocytes; but their results show a wide variation. This makes the testing of mutagenic and carcinogenic agents problematic. A more basic problem encountered in using the SCE technique is that the yield of differentially stained chromosomes is too low for analytical purposes. The present study is designed to standardize the differential staining technique so that the problem of low yield can be overcome. The three specific objectives of this research, are to: (a) establish culture conditions that yield a high frequency of metaphase spreads; (b) determine the time of initiation of DNA synthesis; and (c) establish staining conditions that yield an adequate number of differentially stained chromatids for SCE analysis. (no Refs)

TESTS FOR DNA DAMAGE AND REPAIR

13. INDUCTION OF NEOPLASTIC TRANSFORMATION AND SINGLE STRAND DNA BREAKS IN C3H 10T1/2 CELLS BY POLYCYCLIC HYDROCARBONS AND SHORT CHAIN ALKYLATING AGENTS (MEETING ABSTRACT).

Schechtman LM, Gallagher MA, Henry CJ, Kouri RE, Lubet RA
Microbiological Associates, Bethesda, MD, 20816
Fed Proc; 41(3):379 1982

The known carcinogens benzo(a)pyrene, BaP 7,8-diol, 3-methylcholanthrene, and 7,12-dimethyl benz(a)anthracene, all yielded striking dose-dependent transformation frequencies when tested in the standard 10T1/2 assay. In contrast, the two non-carcinogens anthracene and phenanthrene caused no transformation. The strong chemical carcinogen, dibenz(a,h)anthracene expressed weak transforming activity, while the weak carcinogen, benzo(e)pyrene expressed stronger activity. The short chain alkylating agents N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate induced minimal transformation in the standard 10T 1/2 assay. However, it appears that modification of the assay by replating treated cells post-chemical treatment enhances the ability of the system to identify the short chain alkylating agents. We attempted to optimize carcinogen exposure employing a modified alkaline elution assay (which measures the production of single strand breaks). This test demonstrated few if any DNA strand breaks upon treatment with transforming doses of BaP, or BaP-7,8-diol, whereas significant levels of strand breakage were observed following treatment with minimally toxic non-transforming doses of a number of short chain alkylating agents. (no Refs)

14. A FLUORESCENCE ENHANCEMENT ASSAY FOR CELLULAR DNA DAMAGE.

Kanter PM, Schwartz HS
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Mol Pharmacol; 22(1):145-151 1982

The bisbenzamide fluorescence enhancement assay for measurement of DNA damage in murine leukemia cells is described. In this assay DNA lesions are expressed by time-dependent alkaline denaturation, which results in unwinding points in the DNA. DNA damage, either by frank strand breakage or by introduction of alkaline labile lesions, yields more unwinding points and single-stranded DNA. The amount of DNA present in duplex and single-stranded form can be measured by enhanced fluorescence of DNA induced by bisbenzamide. Calibration with P388 (mouse ascites) and L1210 (tissue-culture adapted) cells demonstrated that the assay was sufficiently sensitive to detect damage induced by 100 rads x-rays. Comparison of numbers of radiation-induced breaks per relative molecular mass of DNA by enhancement assay and hydroxylapatite chromatography gave nearly identical results using L1210 cells exposed to x-rays. P388 cells were placed in short-term culture and exposed for (2-4 hr) to various concentrations of actinomycin D, 1,3,-bis-(2-chloroethyl)-1-nitrosourea, daunorubicin, Adriamycin, carminomycin, bleomycin, 4'-(9-acridinylamino)-methansulfon-m-aniside, hycanthone, and neocarzinostatin, and dose-response relationships were established for all compounds. Of the antineoplastic agents used, only the anthracyclines appear to interfere with formation of the bisbenzamide-DNA complex. (19 Refs)

STUDIES OF ACTIVATION OF CARCINOGENS FOR SHORT-TERM TESTS

15. INFLUENCE OF GLUTATHIONE ON MNNG INDUCED MUTAGENICITY AND TOXICITY IN YEAST (MEETING ABSTRACT).

Eckardt F, Albers M, Summer KH
Dept. of Radiation Biology, Dept. of Toxicology, Neuherberg, W. Germany
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

It is assumed that in vivo the alkylating metabolites of MNNG (N-methyl-N'-nitro-N-nitrosoguanidine) is derived predominantly via a thiol mediated pathway. Since glutathione (GSH) is the major non protein thiol compound it is of interest to establish a correlation between cellular GSH content and the mutagenicity and toxicity of MNNG. We investigated stationary (stat) and logarithmically dividing (log) cells of Saccharomyces cerevisiae, D7RAD, and its excision defective derivative D7rad3. It was found: 1) In stat cells GSH content is higher than in log cells. 2) In stat cells MNNG toxicity is 2-3 times higher than in log cells. 3) In log cells MNNG mutagenicity is not generally lower than in stat cells but shows a complicated dose dependence: at 100% survival the mutagenicity of the log cells is 2 fold higher than in stat cells, but in the toxic range of MNNG it is considerably lower. (no Refs)

16. MUTAGENICITY OF 2-AMINOFLUORENE IN THE PRESENCE OF MICROSOMES FROM VARIOUS RAT TISSUES. CORRELATION WITH KINETIC PARAMETERS OF MICROSOMAL N-HYDROXYLASE (MEETING ABSTRACT).

Fouarge M, Mercier M, Poncelet F
Laboratory of Toxicology, School of Pharmacy UCL 7237, B 1200 Brussels, Belgium
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

N-hydroxylation by a microsomal cytochrome P450 mixed-function oxidases system is an essential step in the metabolic activation of arylamines and in their consecutive mutagenic activities. Usually, liver is the most effective tissue to N-hydroxylate carcinogenic aromatic amines; however, this enzymatic activity was also detected in microsomes of kidney, lung, bladder and small intestine. The mutagenicity of 2-aminofluorene (2-AF), a liver carcinogen, was studied with Salmonella Typhimurium strain TA 1538 in the presence of liver, kidney and small intestine microsomes from untreated rats and rats pretreated with phenobarbital of Aroclor 1254; it was correlated with the kinetic parameters of 2-AF N-hydroxylase. The highest mutagenicity and the higest enzymatic activity (affinity and V max) were observed in the presence of liver microsomes; the lowest mutagenic and enzymatic activities were observed with microsomes of small intestine. (no Refs)

17. HETEROGENEITY OF BENZO(A)PYRENE METABOLISM IN HUMAN AND RODENT CELL CULTURE (MEETING ABSTRACT).

Selkirk JK
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In Vitro; 18(3,part2):289 1982

Cell culture systems are now being routinely used to study the biochemical processing of carcinogens and mutagens. In addition, mammalian cell mutagenesis assays are using lawns of metabolically competent cells as activation systems to produce the reactive electrophile since the testor cells often do not possess the mixed function oxidases containing cytochrome P-450. We have compared benzo(a)pyrene metabolism in rat primary hepatocytes, liver epithelial cells and in normal and malignant human mammary cells. We have monitored the differences in the biochemical processing of the carcinogen in terms of organic-soluble derivatives, water-soluble conjugates and macromolecular binding. In addition, several rodent liver cells were tested as activation systems for the V-70 Chinese hamster cell mutagenesis assay. Significant differences in overall metabolism and pathway variance between human and rodent cells will be discussed. (no Refs)

13. METABOLIC CONVERSION OF GENOTOXIC CARCINOGENS BY UNTREATED AND AROCLOR-TREATED FIBROBLASTS (BHK21/C13) AND HEPATOMA CELLS (MH1CL) (MEETING ABSTRACT).

Badolati GS, Ferro M, De Flora S
Institutes of Hygiene, University of Genoa, Genoa, Italy
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Cultured fibroblasts eg BHK21/C13 cells used in Styles, soft agar transformation assay, are known to be scarcely active in metabolizing xenobiotic chemicals, and are therefore coupled with mammalian S9 fractions for detecting procarcinogens. We have checked whether stimulation with Aroclor 1254 might result in an enhancement of metaboism in BHK21/C13 cells and, in parallel assays, in continuous-line MH1Cl epithelial cells, originated from the transplantable Morris 7795 rat hepatoma. The four carcinogens benzo(a)pyrene (BP), aflatoxin B1 (AFB1), 2-aminofluorene (2AF) and 4-nitroquinolino-N-oxide (4NQO) were used as test compounds and his- strains of Salmonella typhimurium as indicators of their mutagenicity. No mutagenic metabolite of AFB1 was released from intact BHK21 or MH1Cl cell monolayers, whose growth medium had been supplemented either with DMSO (dimethyl sulfoxide) (controls) or Aroclor just after trypsinizaion. S9 fractions were prepared from: rat liver of Sprague-Dawley rats, untreated (24 mg protein/ml) or Aroclor-treated (36 mg/ml); BHK21 cells, untreated (2.4 mg/ml) or treated with Aroclor-10 (2.2 mg/ml) or 1 ug/10(6) cells (2.9 mg/ml); MH1Cl cells, untreated (10.3 mg/ml) or treated with Aroclor-10 (9.6 mg/ml) or 1 ug/10(6) cells (9.9 mg/ml). Aroclor treatment was 48 hr at 37 C in serum-free medium of stationary-phase monolayers. These 8 S-9 fractions were mixed with co-factors and tested at equivalent protein concentration (360 ug/plate) in the Ames plate test (TA98 and TA100). The only significant effect produced by BHK21 fractions was slight reduction of 4NQO mutgenicity. Although less effective than liver fractions, MH1Cl fractions also activated 2AF, such an effect being potentiated by Aroclor stimulation. (no Refs)

19. COMPARISON OF THE ABILITY OF MOUSE HEPATOCYTES AND MOUSE LIVER S-9 TO ACTIVATE NITROSAMINES AND OTHER CARCINOGENS TO MUTAGENIC FACTORS FOR SALMONELLA TA 1535 (MEETING ABSTRACT).

Kerklaan P, Bouter S, Mohn G
Department of Radiation Genetics and Chemical Mutagenesis, Leiden, The Netherlands
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

To assay whether homogenization of liver cells during preparation of S-9 results in a reduction of bioactivating properties, hepatocytes from Swiss albino mice were isolated as suspensions of single cells and their biological activity was determined. Mutagen activation kinetics and cell density dependence for mutation induction were measured with cyclophosphamide (CP) and nitrosodimethylamine (NDMA) and optimal conditions for mutagenesis were determined. Under standardized incubation conditions, CP, NDMA and other carcinogens such as nitrosomethylethylamine and 1,2-dimethyldrazine were mutagenic towards TA 1535 in the presence of hepatocytes. Under those conditions, S-9 prepared from the same mouse strain was a less efficient metabolizing system. Nitrosodiethylamine appears not to be significantly activated with any of the two in vitro systems. These results, though preliminary indicate that freshly isolated hepatocytes have greater capacity to activate precarcinogens such as nitrosamines than S-9 preparations do and are, therefore, probably better representative of the in vivo metabolic activity of the liver. (no Refs)

20. COMPARISON OF BENZO(A)PYRENE METABOLISM AND MUTATION INDUCTION IN CHO CELLS USING RAT LIVER HOMOGENATE (S9) OR SYRIAN HAMSTER EMBRYONIC CELL-MEDIATED ACTIVATION SYSTEMS.

Chen DJ, Okinaka RT, Strniste GF
Los Alamos Natl. Lab., Los Alamos, NM
Proceedings of the Symposium on Polycyclic Aromatic Hydrocarbons, held in Columbus, OH, 27 October 1981. Available from National Technical Information Service, Springfield, VA, as DE82002350:, 8 pp., 1981.

Mutagenesis in CHO cells has been studied by the addition of an enzymatically active liver homogenate (S9) fraction. However, the metabolism of procarcinogens, such as benzo(a)pyrene (B(a)P), by rat liver homogenate differs from that in intact cellular activation systems. Consequently, B(a)P-induced mutation frequencies in mammalian cells may vary when different activation systems are used. This study attempts to compare B(a)P metabolism and conjugation in rat liver homogenate (S9 preparation) and in Syrian hamster embryonic (SHE) cells. Furthermore, a CHO mutation assay incorporating either of the activation systems is being used to measure the mutation induction frequency. (Author abstract)

21. CHEMICAL CARCINOGEN ACTIVATION IN THE RAT MAMMARY GLAND: INTRAORGAN CELL SPECIFICITY.

Gould MN
Dept. Human Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Carcinogenesis; 3(6):667-669 1982

Cells from 50-55 day old virgin Sprague-Dawley female rat mammary gland were divided into parenchymal (epithelial) and stromal enriched populations. The ability of these cells to activate carcinogens was quantitated employing a mediated mutagenesis assay. In addition, the populations' ability to produce water soluble metabolites from these carcinogens was estimated. We report that the potent mammary carcinogen 7,12-dimethylbenz[a]anthracene was activated by both mammary parenchymal and stromal cells, while the non-mammary carcinogen aflatoxin B1 was not activated by either cell type. However, the weak mammary carcinogen benzo[a]pyrene was activated by the stromal cells and not by the parenchymal cells from which mammary carcinomas arise. The data suggest that the intra-organ relationship between cell types that activate a carcinogen, and cell types that undergo neoplastic transformation, may in part help explain the organ specific potency of a carcinogen. (Author abstract) (7 Refs)

22. EFFECT OF AGE ON THE ABILITY OF RAT LIVER TO METABOLIZE THE CHEMICAL CARCINOGEN AFLATOXIN B1.

Jayaraj AA
Illinois State University, Normal, IL
Diss Abstr Int [B]; 42(10):4046-B 1982

The ability of liver fractions from 4-to 30-month-old Fischer F344 rats to activate and metabolize aflatoxin B1 (AFB1) in vitro was studied. The activation of AFB1 was measured by the Salmonella/microsome test and by its ability to bind to DNA in vitro. The metabolism of AFB1 was determined by measuring the conversion of AFB1 to water-soluble and CHCl(3)-soluble metabolites. The activation of AFB1 to compounds that are mutagenic in the Samonella/microsome test and to compounds that bind to DNA in vitro by liver S-9 and microsomes from male Fischer F344 rats decreased approximately 50% with increasing age. The in vitro metabolism of AFB1 by liver S-9 and microsomal fractions decreased significantly with increasing age. The metabolism of AFB1 to water-soluble and CHCl(3)-soluble metabolites was lower for liver preparations from 26-month-old than for 4 and 12-month-old male rats. The proportion of aflatoxicol produced by liver S-9 from male Fischer F344 rats increased approximately two-fold between 4 and 26 months of age. This increase could potentially increase the sensitivity of the organism to AFB1-induced hepatocarcinogenesis. Liver microsomal cytochrome P450 decreased approximately 50% between 4 and 26 months of age. A 60% decrease in the benzopyrene hydroxylase and benzphetamine demethylase activities was observed between 4 and 26 months of age. No age-related change in the ability of S-9 fractions from the liver of female Fischer F344 rats to activate AFB1, to its metabolites that are mutagenic in the Salmonella/microsome test was observed. (no Refs)

23. BEEF EXTRACT MUTAGENS, AND NOT LIVER S9, INCREASE MUTATION FREQUENCY IN THE AMES TEST.

Dolara P
Dept. Entomology, Univ. Wisconsin, 237 Russel Laboratories, 163 Linden Dr., Madison, WI, 53706
Mutat Res; 104(6):345-346 1982

A recent report (Mutation Research 103:263-266, 1982) of higher background mutation rates observed when liver S9 preparations were added to the plates in standard Salmonella-microsome mutagenesis assays is discussed. While the observation is correct, and not new, the suggestion that S9 increased mutation rates in the absence of any added mutagen is incorrect. Indirect-acting agents in the incubation media are responsible for the observed increase of background mutation rates. (9 Refs)

COMPARATIVE TEST RESULTS

24. L5178Y TK+/- MOUSE LYMPHOMA CELL MUTAGENESIS ASSAY OF FORTY CODED COMPOUNDS: RESULTS FROM TWO LABORATORIES AND COMPARISONS WITH RESULTS FROM OTHER BIOASSAYS (MEETING ABSTRACT).

Caspary W, Mitchell A, Rudd C, Mylr B, Lee YJ, Poulton S
National Institutes of Health, Bethesda, MD
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

The mouse lymphoma cell mutagenesis assay is being evaluated in 2 laboratories using a common protocol to test coded compounds. Forty compounds representing one or more of 24 chemical classes have been tested in both laboratories with greater than 95% agreement. These results are compared with NTP (normal temperature and pressure) results from other assays including Salmonella, in vitro UDS in rat hepatocytes, assays of transformation in BALB/c 3T3 cells and in the rat retrovirus system, and in vivo bioassay testing. Thus far, 17 compounds have been tested in all six assays; 10 in at least five of the assays; 9 in at least 4 of these assays, including the mouse lymphoma assay. Positive results were obtained for 2-nitro-p-phenylenediamine, benzo(a)pyrene and 4,4'-methylene-bis-(2 chloroaniline) in 6 of 6 assays; 1,2,3,4-diepoxybutane, cyclophosphamide and ethylene dibromide in 5 of 6 assays; benz(a)anthracene, Michler's ketone and 4,4'methylenebis-(N,N'-dimethyl)benzene and calcium chromate in 5 of 5 assays; and 7,12 dimethylbenzanthracene and 4-nitroquinoline-N-oxide in 4 of 4 assays. N,N-dicyclohexylthiourea was negative in all systems except the 2 transformation systems. Amitrole was negative in the lymphoma and Salmonella but positive in the rat retrovirus and in vivo assay. Dyrene, diethylstilbestrol, lithocholic acid, aniline, anthracene, thioacetamide, methoxychlor and natulan hydrochloride are positive in the mouse lymphoma system and negative in the salmonella assay. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

25. ANIMAL-HUMAN STUDIES. AN INTEGRATED APPROACH TO IDENTIFYING HAZARDOUS CHEMICALS IN THE WORKPLACE (MEETING ABSTRACT).

Legator MS, Ward JB
The University of Texas Medical Branch, Galveston, TX, 77550
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

An alternative approach to evaluating carcinogenic-mutagenic agents by individual procedures is to combine several mutagenic endpoints in a single animal study, 'combined testing protocol'. This same strategy of performing several studies after exposure to a potential mutagen-carcinogen can be carried out in man where urine, blood and semen are used to perform a series of mutagenic studies. The specific procedures that can be carried out in man include metaphase analysis, sister chromatid exchange studies, analysis of urine for agents that induce gene mutations, alkylation of macromolecules, sperm morphology analysis and determination of frequency of extra Y body in sperm. In evaluating a specific chemical, the combined testing protocol in both experimental animals and man, should yield meaningful quantitative and qualitative data in the most efficient manner. In certain instances, animal data can indicate the most appropriate protocol to use in man, ie, body fluid analysis, alkylation of macromolecules. (no Refs)

26. THE USE OF SHORT-TERM TEST RESULTS FOR HUMAN CANCER RISK ASSESSMENT (MEETING ABSTRACT).

Yamasaki H
International Agency for Research on Cancer, F-69372 Lyon cedex 08, France
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

More than 100 short-term tests for detecting potential chemical carcinogens and mutagens are now available. However, it appears that no single test is sufficient for detection of all carcinogens and, therefore, major effort is being made to develop a battery of tests to fulfill this aim. Since our final goal is to detect all chemicals which are hazardous to humans, there exist many barriers in the extrapolation of short-term test results. IARC recently convened a working group which discussed the usefulness of short-term test results for evaluating the carcinogenic risk of chemicals to humans. It was generally agreed that the results from validated short-term tests are useful as additional evidence in interpreting ambiguous data from experimental or epidemiological studies. However, in view of the limitations of current knowledge about mechanisms of carcinogenesis, it was emphasized that these test results should not be used by themselves to conclude whether or not an agent is carcinogenic. Upon these considerations, whenever available, the short-term test results were critically examined together with animal experimental and epidemiological data for the evaluation of over 120 chemicals. (no Refs)

27. THE PREDICTABILITY OF ANIMAL BIOASSAYS (MEETING ABSTRACT).

Anderson D
BIBRA, Woodmansterne Road, Carshalton, England
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Laboratory models which provide data for predicting the potential human mutagenic or carcinogenic risk of chemicals are short-term tests, animal studies or cellular responses combined with human exposures. The efficiency of the models can be judged by their ability to predict a human mutagen or carcinogen, its potency and organ specificity. Cigarette smoke, vinyl chloride, lead and anesthetic gases have the best documented evidence of possible mutagenic effects in man. There are 26 agents which are known to produce cancer in man but only 19 of these are specific chemicals which are also known to be animal carcinogens. Laboratory models are generally judged on interspecies comparisons involving species other than man. Short-term tests can have as high as 90% predictivity for animal carcinogenicity but this is influenced by chemical selection and test conditions. Comparisons in rats and mice of carcinogenicity data show these species to be 85% predictive for each other. About 60% of human carcinogens have the same target organ in man and animal studies. Sixty-five percent of chemicals carcinogens in rats and mice have a common target organ in both species. Short-term tests are not sufficiently developed to predict organ specificity. Potency correlations from short-term tests to animal models are subject to inaccuracies partly because of the variables associated with methods expressing dose and response in animal studies. (no Refs)

28. CHARACTERISTICS OF CARCINOGENESIS - RELATIONSHIP TO BIOASSAYS FOR AIRBORNE MUTAGENS AND CARCINOGENS (MEETING ABSTRACT).

Sivak A
Biomedical Sciences Section, Arthur D. Little, Inc., Cambridge, MA, 02140
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

In order to develop assay procedures to assess the potential risk of developing cancer from exposure to single chemical agents and mixtures, it is necessary to understand the characteristics of the carcinogenic process in vivo. With such an understanding, it is possible to select assay procedures that are soundly based with respect to the response actually being measured and the risk assessed. The induction of cancer is generally the result of multiple factors that impact living systems over a relatively long time span in relation to life expectancy, and the carcinogenic process itself is a sequential one with identifiable stages. The relationship of the induction of these stages (initiation, promotion, progression, etc) to genetic and non-genetic events is a key factor in the use and interpretation of assay results. Procedures to measure a variety of genetic events and some non-genetic ones are available. While the test procedures to examine the putative non-genetic components of the carcinogenic process need considerable additional development and validation, the application of these sorts of assays along with the genetic assays already available can provide information to understand the biological effects of exposure to complex environmental substances such as substances in ambient air or combustion-related air samples. Moreover, these assays can provide assistance in identifying specific biological activities associated with subfractions of these environmental samples and thereby aid chemists in their efforts to identify the individual chemical constituents responsible for potentially detrimental health effects. (no Refs)

29. USE OF GAMMA-GLUTAMYL TRANSPEPTIDASE-POSITIVE FOCI IN SHORT-TERM BIOASSAY FOR CHEMICAL CARCINOGENS (MEETING ABSTRACT).

Pereira MA
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

Gamma-glutamyl transpeptidase (GGTase)-positive foci have been proposed to possess the properties of being preneoplastic and predictive of cancer incidence. Therefore, the induction by a chemical of focal GGTase activity has been proposed to indicate carcinogenic activity of the chemical. However, conclusive proof has yet to be obtained of the preneoplastic nature of GGTase-positive foci. The ability of these foci to predict the future occurrence of cancer is supported by the fact that most carcinogens (including hepatic and non-hepatic carcinogens) can be demonstrated to induce GGTase-positive foci while non-carcinogenic analogues are inactive. The limited data relating the quantitative relationship of GGTase-positive foci and cancer incidence would indicate that over 1000 foci are present for every hepatocellular carcinoma. The applicability of GGTase-positive foci in carcinogenicity testing is as an indicator of carcinogenic activity in short-term initiation/promotion bioassays. These initiation/promotion bioassays are used in level-2 of a three level decision tree approach to carcinogenicity testing. The function in the decision tree of level-1 is to screen chemicals and substances for possible carcinogenic activity; level-2 is to confirm absolutely carcinogenic activity and level-3 is to quantitate the carcinogenic activity. The proposed bioassays for level-2 include 1) rat liver foci bioassay with GGTase-positive foci as the indicator of carcinogenic activity, 2) Strain A mouse lung adenoma bioassay and 3) mouse skin initiation/promotion bioassay. Each of the three bioassays is being evaluated with carcinogens representing the different chemical classes in order to determine the number of false negative and positive. The number of mistaken classification is also being determined for the proposed level-2 set of bioassays as a whole. (no Refs)

30. ANALYSIS OF THE COST-EFFECTIVENESS OF TIER TESTING FOR POTENTIAL CARCINOGENS (MEETING ABSTRACT).

Lave LB, Omenn GS, Heffernan K, Dranoff G
Brookings Institution, Washington, DC
1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 11 pp., 1982.

Several tier-testing frameworks have been developed to screen the thousands of chemicals that are potential hazards to workers and the general public. We present a systematic approach to the analysis of cost-effectiveness that utilizes the sensitivity, specificity, accuracy, cost, and time for each screening test. Parameters are estimated from data from numerous short-term tests in five categories of assays performed on up to 42 selected chemicals (25 presumed carcinogens and 17 non-carcinogens) in 55 laboratories as part of an international collaborative study organized under MRC, ICI, and NIEHS auspices and published by DeSerres and Ashby (Elsevier, 1981). A tier-testing framework is proposed to combine screening for various mechanisms with cost-effectiveness. (no Refs)

31. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.

Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

Chemical induction of brain tumors, current methods for evaluating the carcinogenic potential of chemicals, and possible mechanisms of neuro-oncogenesis are reviewed. Chemical induction of brain tumors by polycyclic aromatic hydrocarbons, nitroso compounds, acrylonitrile, and other chemicals (1-aryl-3,3-dialkyltriazenes, 1,2-diethylhydrazine, azoethane, azoxyethane, and procarbazine) is described. Only a small number of chemicals that induce brain tumors have been identified by routine bioassays of new chemicals. Current guidelines require exposure of a minimum of 50 animals of each sex to 2-3 exposure levels and an equal number of controls. Complete necropsies, diagnosis by an experienced histopathologist, and confirmatory histochemical techniques are essential for properly classified brain tumors. Knowledge of normal variation in tumor incidence between species, strain, and sex is required. A positive bioassay should induce a significantly increased incidence of tumors in a dose-related manner. Possible mechanisms involved in neuro-oncogenesis have been proposed, including the formation and persistance of O6-alkylguanine in brain DNA of rodents and the occurrence of glial cell replication in the presence of promutagenic DNA damage. (48 Refs)

32. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART A.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part A. New York, Marcel Dekker Inc., 273 pp., 1981.

Specific laboratory procedures and techniques commonly used in the study of DNA damage and its repair are reviewed. Methods for detecting radiation products in DNA, including assays for pyrimidine dimers, direct identification of other radiation products, and the use of enzyme probes in detecting radiation products are described. Assays for determination of chemically induced DNA damage and purification procedures for enzymes used in DNA repair studies are presented. Assays of radiation products in DNA are discussed with respect to direct identification of pyrimidine dimers in DNA (paper chromatography, one-dimensional thin-layer chromatography, ion-exchange chromatography, immunocytological detection, nuclease digestion), direct identification of other radiation products in DNA (thymine damage induced by oxygen radical species, cross-links formed by 4,5'-trimethylpsoralen and light, and DNA-protein cross-links), and enzyme probes for detecting radiation products in DNA (endonuclease V of bacteriophage T4, Micrococcus luteus extracts, x-ray damage in supercoiled DNA). DNA damage produced by chemicals may be assayed by measurement of alkylation products, measurement of formation and removal of adducts of N-acetoxy-N-acetylaminofluorene, repair of base damage caused by 7-bromomethylbenz(a)anthracene, measurement of base damage caused by 4-nitroquinoline 1-oxide, and measurement of alkali-labile sites and sites of base loss. Enzyme preparation for DNA repair studies is discussed with respect to purification of Escherichia coli photoreactivating enzyme, endonuclease V of bacteriophage T4, the major AP endonuclease of E coli, uracil-DNA glycosylase of Bacillus subtilis, and hypoxanthine-DNA glycosylase of calf thymus. (388 Refs)

33. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART B.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

DNA repair technology is reviewed with emphasis on application for research and development purposes. Measurement of DNA repair synthesis by autoradiography, equilibrium sedimentation, photolysis of bromouracil, benzoylated naphthoylated diethylaminoethyl cellulose, and metabolic inhibitors is described. DNA strand breaks can be measured by sedimentation in alkaline sucrose gradients, alkaline elution, alkaline denaturation and hydroxyapatite chromatography, electron microscopy, gel electrophoresis, end labeling, and nitrocellulose membrane filtration. DNA daughter strand repair can be measured by postreplication repair in prokaryotes and mammalian cells, alkaline elution, and bromouracil photolysis. Biological parameters of DNA repair are discussed with respect to measurement of colony-forming ability and mutagenesis in diploid human cells and Chinese hamster cells; genetic markers for mutagenesis studies in mammalian cells; screening of mutagens by inhibition of DNA synthesis; measurement of sister chromatid exchange in mammalian cells; and purification, plaque assay, and inactivation of human adenoviruses 2 and 5. (491 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.
Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.
Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.
Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).
Furst A
Institute of Chemical Biology, University of San Francisco, San Francisco, CA, 94117
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

5. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.
Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
Mutat Res; 99(2):129-242 1982

RADIATION CARCINOGENESIS

6. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 1.
Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services Facility, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 1. Washington, D. C., U. S. General Accounting Office, 85 pp., 1981.

7. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 2.
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Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 2. Washington, D. C., U. S. General Accounting Office, 690 pp., 1981.

8. RISKS OF NUCLEAR ENERGY AND LOW-LEVEL IONIZING RADIATION. REPORT OF AN AMA ADVISORY PANEL TO THE COUNCIL ON SCIENTIFIC AFFAIRS OF THE AMERICAN MEDICAL ASSOCIATION.
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Dept. Nuclear Medicine, St. Elizabeth's Hosp., Boston, MA
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10. EVOLUTION OF THE CONCEPTS AND STANDARDS OF RADIATION PROTECTION.
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11. IONIZING RADIATIONS: DNA DAMAGE, MUTAGENICITY AND MORPHOLOGICAL TRANSFORMATION IN MAMMALIAN CELLS. CARCINOGENICITY IN RODENTS AND IN HUMAN.
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12. CONTROLLING CADMIUM IN THE HUMAN FOOD CHAIN: A REVIEW AND RATIONALE BASED ON HEALTH EFFECTS.
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13. THE EPIDEMIOLOGY OF CANCER IN CHINA.
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16. RELEVANCE OF COLONIC MUCOSAL INFLAMMATION TO AETIOLOGY.
Earnshaw P, Busuttil A, Ferguson A
Gastrointestinal Unit, Univ. Edinburgh, Edinburgh EH4 2XU, England
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18. ACUTE MYELOID LEUKEMIA FOLLOWING TREATMENT OF HODGKIN'S DISEASE. A REVIEW.
Grunwald HW, Rosner F
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Trau H, Schewach-Millet M, Fisher BK, Tsur H
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20. HEALTH EFFECTS OF EXPOSURE TO DIESEL EXHAUST: IMPACTS OF DIESEL-POWERED LIGHT-DUTY VEHICLES.
Griffin HE, Brusick DJ, Castagnoli N, Crump KS, Goldschmidt BM, Higgins IT, Hoffmann D, Horvath SM, Nettesheim P, Stuart BO, Witschi H
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Johnson FC
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24. DNA MODIFICATION AND REPAIR IN THE EXPERIMENTAL INDUCTION OF NERVOUS SYSTEM TUMORS BY CHEMICAL CARCINOGENS.
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DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

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27. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).
Hill DL, Grubbs CJ
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31. POSSIBLE IMMUNOLOGICAL MECHANISMS IN C-TYPE VIRAL LEUKEMOGENESIS IN MICE.
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Oriel JD
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Blumberg BS, London WT
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Stavrou D, Bilzer T, Hulten M, Zanker KS, Anzil AP, Haglid KG, Dahme E
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Mutat Res; 99(2):243-255 1982

37. METABOLIC AND MODULATING FACTORS IN TOXICITY AND CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).
Fishbein L

National Center for Toxicological Research, Jefferson, AR

1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

38. PROCEEDINGS OF THE INHALATION TOXICOLOGY AND TECHNOLOGY SYMPOSIUM HELD IN KALAMAZOO, MI, 23-24 OCTOBER, 1980.

Leong BK

Industrial Toxicology Lab., Upjohn Co., Kalamazoo, MI, 49001

Proceedings of the Inhalation Toxicology and Technology Symposium held in Kalamazoo, MI, 23-24 October, 1980. Ann Arbor, MI, Ann Arbor Science Publishers, Inc., 313 pp., 1981.

39. CHEMICAL CLASS SEPARATION AND DETAILED IDENTIFICATION OF GENOTOXIC POLYCYCLIC AROMATIC COMPOUNDS IN AIRBORNE PARTICULATES (MEETING ABSTRACT).

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Department of Chemistry, Brigham Young University, Provo, UT, 84602

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OTHER REVIEWS IN CARCINOGENESIS

40. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

Nunziata A, Storino AA

Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy

Vet Hum Toxicol; 24(4):243-247 1982

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